UNIVERSITY OF BERGAMO
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DIVERGENT THINKING IN ATYPICAL PARKINSONISM

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ABBREVIATIONS

- PD: Parkinson's Disease
- PSP: Progressive Sopranuclear Palsy
- MSA: Multisistemic Atrophy
- CBD: Cortico-Basal Degeneration
- AD: Alzheimer's Disease
- DA: Dopamine
- DATh: Dopaminergic Therapy
- L-Dopa: Levodopa
- MMSE: Mini Mental State Examination
- CDT: Clock Drawing Test
- FAB: Frontal Assessment Battery
- DT: Divergent Thinking
- ATTA: Abbreviated Torrance Test for Adults
- TTCT: Torrance Test for Creative Thinking

ABSTRACT

Creativity is strongly dependent on divergent thinking and divergent thinking appears to be strongly linked to frontal lobe function. Since Parkinson's disease (PD) depends also on a dysfunction of the frontal lobe, with this research we aim to investigate if a change in the divergent thinking of patients with this diagnosis can be observe. Moreover, since the atypical parkinsonism is a group of neurodegenerative diseases involving the combination of parkinsonian symptoms and other neurological signs, we would make a comparison between atypical parkinsonism (PKS) and PD cognitive and creative level.

An appropriate battery of neuropsychological tests was given to 13 patients with idiopathic PD, to 13 multiple system atrophy (MSA) patients, to 13 patients with progressive sopranuclear palsy (PSP) and 13 normal control subjects (HC). An exploratory survey on 4 corticobasal degeneration (CBD) was conducted too. The Abbreviated Torrance Tests of Creative Thinking for Adults (ATTA), a known test assessing creativity along the dimensions of fluency, flexibility, originality and elaboration was used to examine divergent thinking. Nobody of the subjects plays a creative work.

Comparing all the data we found that creative PSP level is lower then other groups. Instead, the creative PD and HC level are similar. The result seems to confirm the central role of frontal lobes in creativity. In particular, we hypotesize the involvement of dopaminergic midbrain circuits and limbic system while the role of dopaminergic treatment remains doubtful.

To people I love:

my husband and my daughter

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1. INTRODUCTION

When trying to define Creativity, commonly, we said that is to add something original to what already exists. Although this definition of Creativity may appear limited, the originality is certainly a very important aspect of creative thinking. To be original creative people has to take a different direction from the prevailing mode of thought and expression: this ability is known as divergent thinking. There are two components of divergent thinking: the disengagement from current solutions and the development of alternative solutions.

Several studies converge in supporting that frontal lobes are important for the disengagement skills and developing new strategies for action. In fact, humans and non-human primates' frontal lobes are involved in regulation of many aspects of adaptive behavior to the environment and, in general, to the control of higher cognitive processes which operate in everyday complex situations and in unusual contexts. These cognitive processes are defined executive functions; lesions of the different regions of frontal lobe, or fronto-subcortical circuits, determine very different clinical pictures between them.

Fronto-subcortical degenerative diseases are characterized by cognitive impairment, behavior and personality, as well as movement disorders. Among these conditions there are Parkinson's disease and a group of neurodegenerative diseases defined atypical parkinsonism, which differ from Parkinson's disease for the presence of additional neurological symptoms, to a lesser response to pharmacological treatment with L-DOPA and for a more rapid evolution.

With this research, we wanted to study the correlations between Parkinson's Disease, Parkinsonisms, Creativity and frontal lobes. All research subjects were evaluated in two ways by means of neuropsychological and divergent thinking, measurable aspects of the construct of creativity.

The obtained data, indicate that the areas of frontal lobes, the dopaminergic midbrain circuit and their projections to limbic system, are involved in creative process. As for the role of dopaminergic therapy, our results highlight however once again its ambiguous character.

2. THE CREATIVITY

2.1. Definitions of creativity

For a long time, the ability to create was considered a magical power reserved only for outstanding individuals: a prerogative of the few. Others were part of the indefinite bulk of ordinary people, who only had the opportunity to consume the genius' products. Only thirty years ago, American researchers first and Europeans then started to take an active interest in creativity. In fact, the classical intelligence "convergent" call is a brain's working model, artificial model (but not negatively considered) which allows you to travel easily on paths already traced by experts and consolidates power.

Creativity, as a way to innovate, is relatively recent. If it has its ancestors in Europe with Heraclitus, Socrates, Leonardo, Descartes ("The reason is nothing without imagination"), in the United States it takes a structured form as a searching method of innovative ideas for companies.

In Europe first came the *brainstorming* that attracted attention as a capable method to transform imagination in a constructive approach. This apparently simple technique was poorly productive without proper training. Its success was relative. Creativity continues to keep something ambiguous, to be admired as the mother of all virtues, and to be feared because supposed to be the origin of all disturbances and errors. About this, Poincaré (mathematician) wrote: "The soul's mess is the necessary condition for the fruitfulness".

Extremely important and revolutionary was the J.P. Guilford's work and his research on the creative potential, namely talent.

What happens in our brain when we turn on the light bulb intuition? Is it a magical moment, a kind of enlightenment, or rather the blossoming of an idea as the result of a long silent extemporaneous preparation? How to differentiate good insights from the useless ones? The dynamics of the mysterious phenomenon, which we call generically creativity, was always, especially in Occidental culture, the center of a lively interest, which has been driven by discussions, not only in scientific hypotheses and research. Today the focus on this particular mind and human nature's aspect reached very high levels and contemporary society attaches unprecedented value to the creative potential of individuals, in its broadest sense: from manifested fantasy in childhood up to

scientific research, from the many forms of artistic expression to the production of goods, both technological and not. However, the term creativity is volatile, ambiguous and too often improperly used. What are we really talking about when we talk about creativity?

Creativity construct received much interest from various disciplines such as psychology and neuroscience. The reason may be due to the fact that creativity is a complex mental process and therefore difficult to study. Numerous researchers didn't only define the creativity in different ways, but approached studies using different paradigms, providing different explanations to the mechanisms, underlying the creative thinking.

There is no agreement on the definition of creativity, neither among part of the experts, or among researchers.

Creating properly means producing something (object, idea, structure) that it appears to the most as new or original. It is not easy, in fact, to define exactly what constitutes the creativity. In the above definition it is clear how creativity involves to do (the produced new "objects") that must be reviewable by the judgments of others. This judgment provides a criterion of the created product' *novelty*, and this also implies a *tradition'*s policy, by comparison with the object which may or may not appear original.

Another implicit criteria in judgment around the *creative* character of a product is its usability by third parties. Not everything which is new is, in fact, equipped with the requirement of being creative. Only what effectively responds to a need, that is purely aesthetic (artistic creation) gets the product's recognition *creative*.

Creativity as a human action thus refers to a complex interplay of individual (the characteristics that make an individual capable of creativity), social (the consensus around the criteria that allow the recognition of the creative effort, and their prize), and cultural (the notes of complex knowledge, handed down as tradition) factors. All these elements, in various ways, help to define the boundaries of creativity as human capacity.

From socio-biological point of view, Creativity is one of the cognitive functions which contribute to the adaptation of evolution. Human being is the only animal who can, more than any other, *create* his own world, their own environmental space, transforming even people's environmental space (the other species), in this process.

Csikszentmihalyi and Csikszentmihalyi (1988) presented a detailed analysis of how value and novelty are both relevant for creativity. A new product becomes creative only after becoming part of the domain, and then, only after it was positively assessed by the relevant area. In this perspective, if the product is rejected by field, that product is not creative, regardless of whether it is new or not. Some authors (Weisberg, 1993; Heilman, 2005), however, do not agree with the concept that the products should be positively evaluated to be considered creative. Often, a product is not enhanced in the moment in which it is produced but is reassessed by successive generations, or vice versa. For example, Impressionists were criticized when they began painting and Galileo Galilei was seen as a heretic and imprisoned when he first supported the heliocentric Copernicus' theory.

For all these reasons, it may be useful separating the creativity of the product by the value of the product and consider a product as a creative if it is new and produced intentionally.

Cesa-Bianchi et al. (2009) propose a multi-dimensional definition of creativity:

> "Creativity, in science, in the arts or in daily activities, can be defined as the ability to invent ideas or objects, discovering new perspectives for interpreting reality, conceiving original and innovative solutions, or simply finding better ways of doing things. Or, it is the ability of connecting ideas and reasoning levels different from each other, connecting what is usually separated, or producing new points of view. Creativity is therefore an adaptation tool, without which man could not develop alternatives to the present, could not imagine the future or could not read the past."

2.2. Creativity and psychology

Psychology gave an essential contribution to the study of Creativity.

The creative processes begun to be studied in a scientific way in the fifties, when some research institutions were founded, whose main purpose was developing this theme. From that time onwards, research was diversified in this field and every school of thought developed its own theory.

In the psychoanalytic perspective, represented by Freud, Jung, Rank, Klein, Winnicott, Erickson and more recently by Segal, Kris, Kubie and Rams, Creativity was interpreted as the ability to use unconscious or preconscious content, such as sublimation or deviation of the libido, unsatisfied wishes' compensation or ability to process internal

conflicts and difficulties, turning them into opportunities of growth. Creativity is an expression of the unconscious: creative impulses reflect the need to bring it out, shaping trauma and conflicts and trying to play states of wellness too.

According to the Gestalt psychologists, however, creative thinking - defined productive thinking - is characterized by a vision. This intuition is a sudden, instantaneous and appropriate response, based not exclusively on intuition extemporaneous. Beacause insight is preceded by preparatory moments, followed by a phase of verification of results. The insight structure's attention is what allows the productive thinking of making a restructuring or indeed to seize new properties of the elements of the problem. These properties are well designed and used in new roles or different perspective (Wertheimer, 1945).

The Behaviorism explained, however, that psychological processes as a set of associations between stimuli and responses with the support of reinforcements. It assumes that human action is governed essentially by external phenomena. The Mednick's theory about Creativity (1962) provides an explanation of particular associations between stimuli and responses. These associations are characterized by the fact that the items are related in an unusual way. For Mednick, therefore, the defining characteristic of creative thinking is the ability to associate ideas.

Weisberg (1986), insted, considers the creative subject as an individual who, faced with the problem in which it is engaged, tries to retrieve information from his memory and to develop solutions based on some defined criteria that he, or the context, gave to him. In this light, Creativity is seen as everyday thinking continuing with the past.

In contrast to the behaviorist theories there are the cognitivist theories: the individual becomes an active part, he stops being considered a passive element whose behavior is shaped by the environment around. Creativity is no longer seen as a separate method of associative links, but as a new way to receive, manipulate the associations combining data to find efficient solutions. This current research resulted in the identification of Creativity with problem solving. The cognitivist researchers (Guilford, 1950; Torrance, 1977, Rubini, 1980) produced a large number of maps indicating the cognitive abilities and the constructs support creative activity. An important role is played by meta-cognition, ie the activities of reflection and recognition of own cognitive processes.

Creativity develops and grows through different observational moments, self-observational.

In the personalist vision (Rogers, 1954; Maslow, 1962), creative attitude is considered as expression of the perfect functioning of the individual, due to the achievement of a lasting balance between the various behavioral components. According to Rogers (1954), the key element of creativity is the innate human tendency to develop their potential. On the other hand, according to Maslow (1962), the creative person is one who achieves self-realization of self and this is possible only with the satisfaction of basic needs.

Constructivist theory, finally, brings together the development of creative thinking with the need for active participation in the process itself. According to this theory, learning is reached through exploration, experience and manipulation of objects and materials. Vygotsky (1933) emphasized on adequate interaction between the child and the group of adults and/or peers who encourages, enriches and expands creative possibilities. Later, Piaget (1972), based on his stages theory of thinking's development, establishes a direct link between development of creative thinking and active learning, which involves attention to the interests, inclinations and characteristics of child.

2.3. Creativity and neuroscience

The neural basis of artistic production and Creativity were studied by numerous researchers: philosophers, scientists and artists. Knowing if the talent which produces art has a neurological substrate fascinates anyone trying to understand the different brain functions. In the same way those researchers have been seeking to understand the relationship between the brain and the philosophical concept of mind. There is a tension between the concept of man as a biological entity, whose behavior is dictated by the laws of the natural world, and the idea of soul, unique to each individual and that could find expression through artistic creation. At this point arises an intersting question: is the ability to create art reflecting an unique combination of complex neural networks, or is there some single structure for the artists?

The research based on neurophysiology of the creativity is an arduous work. At the first instance, it meets the difficulty to define exactly what the creativity is and in the second place the knowleges about cerebral functioning are restricted.

It is known from millennia that brain injuries cause alterations in behavior. But only since 150 years scientists have enough knowledge about the relationship between brain, mind and behavior.

The study of brain function is essentially based on three survey methods: stages of development, results of injury, level of excellence in the performance of a particular function. It's just the second way, that applies to the study of the consequences of brain injury, which allowed for the first time science to explore human mind. In 1836 the neurologist Marc Dax described in a report as left-brain lesions were constantly in association with language disorders. This observation was poorly considered for a long time. Only in 1861, the French neurologist Paul Broca reported the case of a patient who, as a result of an isolated injury to the foot of the third left frontal gyrus, had entirely lost the use of language. In 1874 Wernicke described the case of a patient with isolated lesion of the circonvolution of the left temporal (*Wernicke's area*) who had developed disturbances in language understanding. As a result of these and other observations, in 1885 Broca started to state that the language functions were localized in the left hemisphere (Clarke and O'Malley, 1968).

Among the many approaches that have been applied to investigate creativity, the neurobiological approach has a surprisingly long history. The characterization of the brain's response when generating novel responses was achieved through the use of direct and indirect global measures, such as electroencephalography (EEG) and lateralization paradigms (for review, see Martindale, 1999). (In the next section we will deepen the results of some studies on the neurophysiological bases of creativity).

Creativity is an even more complex construct of intelligence, and the difficulty of finding neuropsychological correlates to its expression therefore appears even greater (Abraham, 2013). Creativity is commonly defined as a personal process aimed to the creation of ideas, products judged as new and innovative by a common consensus expressed by a community of experts and a wider audience. The consensus around what constitutes the novelty of creative product has an eminently collective and social approval. The same realization of the creative material produced, even in the pure and simple form of idea or project, requires numerous steps of a social nature. You can not produce objects without access to resources, whether or not consumable. Then the

produced work must be communicated in different form because the judgment about its creative character can take place.

However, beyond the important social dimension of creativity, the creative act is something individual, even when it is expressed in a collective dimension, as it happens more and more often in medical scientific research or in some artistic fields (theater, cinema, multimedia production). Many aspects of creativity are therefore likely to be investigated at individual level, and it is already now possible to draft a "neuropsychology of creativity" that takes into account individual differences and aspects, which may be developed through practice and teaching.

2.4. Creativity and connetivity

Since Paul Broca's study (1863), it was repeatedly shown that the brain is organized on a modular basis. Creativity, then, might require communication between modules. Probably, the most obvious evidence of brain modularity is hemispheric specialization: left hemisphere is dominant for language, even in the most left-handed people, for motor control and for processing categorical.

In contrast, right hemisphere is important in spatial cognition, including the spatial imagery, recognizing faces and coordinated encoding. Right hemisphere also seems to be important in emotional communication and may also be dominant in the mediation of many primary emotions (Heilman et al., 2000). Furthermore, while right hemisphere seems to have global importance in attention (Robertson et al., 1988; Barrett et al., 1998), left hemisphere appears to be important in focus attention.

Creativity requires that you use the skills and knowledge mediated by both hemispheres. For example, a novelist who is describing his character's emotions must use knowledge of facial emotional expressions stored in right hemisphere with the verbal lexicon stored in left hemisphere. A sculptor has to imagine pictures of the rotation of space mediated by right hemisphere, while using motor skills mediated by the left one.

Thus interhemispheric communication might be important to combine knowledge and skills and important for creative innovation. Since both hemispheres store various forms of knowledge and mediate different forms of cognitive activity, there are probably different neural architectures within associative cortices of either of the lateral halves of brain. A possible resolution to an unsolved problem would be to see this problem in a

"new light", using a different form of knowledge and a different cognitive strategy that could be mediated by opposite hemisphere of the one used previously.

The largest structure, which connects independent modular systems, is the corpus callosum. Lewis (1979) administered the Rorschach Test in eight patients who suffered a brain commissurotomy, to treat a severe form of epilepsy. He observed that the disconnection of the two cerebral hemispheres tended to destroy creativity. Bogen and Bogen (1988) noted that, although the corpus callosum can transfer high-level information, normally this interhemispheric communication is incomplete. Bogen and Bogen postulated that the incomplete interhemispheric communication allows independence and lateralized hemispheric knowledge, important in the incubation stage of ideas. These authors mentioned Frederic Bremer, who suggested that the corpus callosum, for its function's connection, makes the highest and most elaborate brain activity, in a word: Creativity. They also suggested that the temporary suspension of this partial independence explains illumination's phase.

The corpus callosum is mainly composed of myelinated axons whose cell bodies are located in the pyramidal strata of the cerebral cortex. Brain connectivity, important for creativity, could be not only interhemispheric but also intra hemispheric. In addition to myelinated axons which carry information between both hemispheres, the thalamus and the basal ganglia to the cortex and from cortex to the basal ganglia, the thalamus, the brain and spinal cord trunk. These myelinated axons carry information between cortical regions in the same hemisphere too. These intra hemispheric connections facilitate intra hemispheric communication, which could also be important for creative innovation as the widespread connectivity would allow creative people to combine the representations of previously isolated ideas (Heilman et al., 2003).

In addition, the cerebral cortex has several levels of activity, or better supervision. When we observe high levels of activation, we are in the presence of strong emotions such as fear or anger while during the sleeping we are seeing low levels of supervision. The electroencephalogram, which provides the layout of the electrical activity of the brain, shows that activity is slow and regular when we are in a relaxed state and is fast when we are excited or we're trying to solve a task. When we are passing from wakefulness to sleep, activation decreases and waves are slower and regular.

Electrical waves of brain activity are divided into Alpha waves, typical of the state of relaxation, with a frequency between 8 and 13 Hertz; Beta waves, typical of the state of attention and wakefulness, which have a frequency between 13 and 30 Hertz; Theta waves, which are the waves of drowsiness and fantasy, with a frequency of between 4 and 8 Hertz; Delta waves, typical of the deep sleep stages and are characterized by a frequency ranging between 0.1 and 3.9 Hz.

Creativity occurs primarily with low levels of cortical activity, with an activity of Theta waves (Cesa-Bianchi et al., 2009). Easterbrook (1959) and Eysenck (1995) suggested that the high cortical activation induced by stress is often associated with conscious attempts of solving problems. But this high activation may suppress the emergence of remote associations; then a low level of cortical activation might allow unusual associations to occur.

As we saw, cortical activity in the EEG Alpha band has proven to be particularly sensitive to creativity related demands, but its functional meaning in the context of creative cognition has not been clarified yet. Specifically, increases in Alpha activity in response to creative thinking can be interpreted in different ways: as a functional correlate of cortical idling, as a sign of internal top-down activity or, more specifically, as selective inhibition of brain regions (Fink et al., 2009). The generation of original ideas seems associated with Alpha synchronisation in frontal brain regions and with a diffuse and widespread pattern of Alpha synchronisation over parietal cortical regions. EEG Alpha band synchronization during creative thinking can be interpreted as a sign of active cognitive processes rather than cortical idling, too (*Ibid.*).

A fMRI study revealed an association between the originality component of creativity and reduced deactivation of right parietal brain regions and the precuneus during creative cognition. This finding suggests the idea that more-creative people may include more events/stimuli in their mental processes than less creative people do (Fink et al., 2013). The authors (*Ibid.*) suggest a similar operation mode between the psychotic-schizophrenic and the creative thought.

Another research revealed that verbal creativity is significantly and positively associated with gray matter density in clusters involving the right cuneus and the right precuneus. Enhanced gray matter density in these regions may be indicative of vivid imaginative abilities in more creative individuals (Fink et al., 2013).

2.5. The role of frontal lobes and catecholamines

Creative people have a low level of activation especially in frontal cortex, which when active blocks irrelevant behaviors and not projected to a specific purpose: frontal cortex comes into operation in solving specific problems and discarding mental associations considered unnecessary for purpose (Eysenck, 1995). Thus, less activation of this area favors creative associations (*Ibid*.).

Thanks to the Transcranial Magnetic Stimulation (TMS) experiments, with which you can reduce activation of entire brain areas, it was discovered that if you inhibit the activity of the frontal cortex, associations can be made easier and less trivial. Creativity generally depends on the ability to "silence" frontal cortex in order to emerge with associations and analogies fluidity (Cesa-Bianchi et al., 2009). Catecholamines, dopamine and norepinephrine appear to play an important role in creativity. Stress does not support creativity and is associated with elevated levels of norepinephrine in brain. Sleeping and relaxation being associated with a low level of norepinephrine foster Creativity. The neurological phenomenon of the *hypergraphia* (the compulsive urgency to write) helps locate anatomically creative impulse. This phenomenon was described in some cases of temporal lobe epilepsy (Waxman and Geschwind, 1974). Hypergraphia is generally proposed to reflect decreases interictal activity in temporal lobe. It is more common when lesion is in right hemisphere, probably because left hemisphere, the dominant side in the language, is uninhibited (Yamadori et al., 1986). Temporal lobe epilepsy is not the only brain condition which produces hypergraphia; infact, most patients with hypergraphia have mania and relative states of agitation (Kraepelin, 1921). The maniacal patients show an increase in resting state in SPECT right anterior temporal and quantitative decrease in EEG signal at the lower left in temporal lobe Gyulai et al., 1997; Small et al., 1998). Temporal lobe's changes can produce the equivalent of the hypergraphia in other creative fields too. Fronto Temporal Dementia (FTD) is the best known example. A subset of these patients develops a neurodegeneration which selectively attacks temporal lobe. Up to 10% of this subset develops artistic or musical interests, even when they did not have pre-existing artistic trends (Miller et al., 1998).

The mentioned studies above suggest, according to Flaherty, that temporal lobe can be described as headquarters of the creativity's suppression, because impairment of this

area appears to favor the development of favorable conditions to trigger creative impulse. In creative process the role of the limbic system and the relative production of dopamine are made explicit by several studies. According to the researcher Martindale (1999), creative subjects have elevated levels of basic activation and greater response to sensory stimulation. In fact it has seen that dopamine decreases latent inhibition[1], a behavioral index used to get sensations capacity (Ellenbroek et al., 1996; Swerdlow et al., 2003). In this way, a low latent inhibition can flood a body of stimuli, as also seen in psychoses (Swerdlow et al., 1996). But the low latent inhibition is also a characteristic of creative individuals with high intelligence (Carson et al., 2003).

Dopamine is not limited only to raise basic excitement. The creative impulse can be operated mesolimbic dopaminergic activity. The mesolimbic pathway connects the ventral tegmental area to the nucleus accumbens through the amygdala and the hippocampus (both at the center of the reward system in the brain). It is thought that this pathway controls behavior and especially produces delirium and hallucinations when overactive. It is also the way which regulates the sense of gratification, involved in addiction's phenomena. Whereas dopamine agonists can induce hypomania and hallucinations (Peet & Peters, 1995), dopamine antagonists, generally used as antipsychotics, are known for their ability to suppress not only the hallucinations and stereos, but also Creativity.

Temporal lobe plays an important role in the interaction between dopaminergic drugs innovative thought belonged only to the psychotic sphere. Functional magnetic resonance imaging shows that the auditory hallucinations of the schizophrenic (which may resemble experience of having a creative idea dictated by the muse) selectively activate temporal lobe (Shergill et al., 2001). Metaphorical thinking is selectively impaired by temporal lobe lesions (Jakobson and Halle, 1972). Although metaphors, when vivid enough, may be a step toward the psychotic delirium spectrum ("I suffer like Jesus" becomes "I am Jesus"), the metaphorical thought is still vital for Creativity, because the metaphore from the identification of similarities between previously unrelated phenomena depends. This applies both to the non-literary creativity and to

[1] Latent inhibition refers to the retarded acquisition of a conditioned response that occurs if the subject bein tested is first pre-exposed to the to-be-conditioned stimulus without the paired unconditioned stimulus.

writers. Even the scientific models are metaphors which enable predictive power (Martindale, 1999).

The frontal lobe's function is discussed in the article by the lack of creative drive. In fact there seems to be a positive correlation between the dysfunction of the frontal lobe and the creative block.

The first condition which connects frontal dysfunction and creative block is depression. Many techniques, including functional imaging and analysis of lesion, have shown deficits in frontal depression. During the depression, motivation and cognitive flexibility decreases, as well as tasks aimed such as feeding and sexual activity (Jamison, 1989; Flaherty, 2004).

The second condition of frontal lobe similar to writer's block (especially the writer's block) is a lesion in Broca's area. The Broca lesions produce a selective deficit in the production of language, in contrast to the problems of understanding the speech of Wernicke aphasia. Although the writer's block is not aphasia or an *agraphia*,it shares with Broca's aphasia characteristics as the awareness of the errors of speech and the reduction of speech production.

A third group of conditions, i.e. frontal lesions outside of Broca's area, can cause depression and the decrease of the speech independently from aphasia. The lesions of the frontal lobe can cause cognitive deficits such as perseveration which are similar to the stubborn and unproductive efforts of blocked writers.

Anxiety and depression are the fourth condition. These show changes in frontal lobe in a number of paradigms (Cannistraro & Rauch, 2003). Anxiety, furthermore, is highly associated with the creative block.

Fifth, the characteristics of the writer's cramp (focal dystonia which shows changes in the sensorimotor and premotor cortex (Lehericy et al, 2003)) suggest that there may be an analogy with writer's block in the posterior frontal motor areas. Writer's cramp, such as blocking, seems to be induced by highly repetitive practice and stressful task (Byl et al., 1996).

Sixth, electromagnetic studies show that the functioning of frontal lobe stimulates Creativity. Comparing subjects with high and low creativity, it was verified that the former has greater frontal lobe activity when performing creative tasks but also at rest. (Carlsson et al., 2000). There is evidence that transcranial magnetic stimulation on the

frontal lobes can increase Creativity in normal subjects in drawing tasks and in writing tasks (Snyder et al., 2004). There are reports of patients whose creativity increased after the deep subcortical brain stimulation with electrodes placed near the nucleus accumbens (Gabriels et al., 2003; Flaherty et al., 2005). The connections of the nucleus accumbens with frontal and temporal lobes, and its role in limbic generation of pulses, may help to explain this effect.

In conclusion, according to the authors (Flaherty, 2004; Flaherty et al., 2005), creative drive has the advantage of being a simpler and more manageable phenomenon of Creativity itself. The creative impulse connections more understandable systems, such as the impulse to communicate, provides both direct and indirect evidence for an anatomical three-factor model of the creative force which coordinates frontal, temporal and limbic systems. It is suggested that the fronto-temporal interactions are probably mediated by mutually inhibitory corticocortical projections, while limbic contribution is linked mainly to dopamine.

As already mentioned, there was an intense interest to determine how brain processes the outside world and to identify the related neuroanatomical areas of the ability to create art. In particular, it was found that there are two basic ways of visual art: the ventral pathway, which is involved in recognizing "what" you are seeing and the dorsal one to locate "where" the objects are perceived. The visual scenes absorbed over a lifetime receive a meaning by ventral pathway's components which locates them in the temporo-parietal cortex. These ones, internally represented by images of people, animals and objects, are the creative ground for many artists, which reproduce them in form of drawings, paintings and sculptures (Miller & Hou, 2004).

The *locus coeruleus* is the main source of norepinephrine output from the cortex. Aston-Jones et al. (1991) postulated that high levels tonic activity of the *locus coeruleus* (which increases levels of norepinephrine in the cortex) would be important for monitoring and participation to external stimuli and increase behavioral responsiveness to new and unexpected stimuli. The *locus coeruleus* is therefore necessary for the activities of "fight-flight". It follows, therefore, that low levels of activity of the *locus coeruleus* improve cognition and creative production (Chakravarty, 2010).

The frontal lobe seem to be able to exert an inhibitory influence on the *locus coeruleus* (Sara SJ. Herve, 1995). So frontal inhibitors behavior would be in favor for creative

tasks. At low levels of disinhibition, the activity of *locus coeruleus* decreases providing reduced levels of norepinephrine in cortex. Facilitates representations of creative thinking and a high level of frontal disinhibition may improve the activity of the *locus coeruleus* causing a high level of norepinephrine in the cortex, which it is not conducive to creativity (Chakravarty, 2010).

The mapping of the human cerebral cortex is one of the ways to determine the related fundamental neuroanatomical of artistic creation. In fact there is a large literature on the effects of strokes and other focal lesions on the artistic production of individuals. However, it was decided to limit the discussion to the indirect insights that you can pick from an examination of the artistic production and its evolution in people with neurodegenerative diseases. The analysis of literature emphasizes the occurence of abstraction, as an emerging feature in neurodegenerative diseases (Kleiner-Fisman & Lang, 2004).

Abstraction was described as the process in which the particular is subordinated to the general, for which what is represented is applicable to many details (Zeki, 2001). The primary role of visual cortex is just to extract essential features and invariant from the environment, and people, with unusual skill in this sense, can be considered artistically talented.

Some researchers argued that the increasing abstraction capabilities in the artistic production reflects an improvement of skills. Others argued that the emergence of abstraction, when it was previously absent, is a manifestation of cognitive and visual-spatial decline.

We will now see, specifically, a review of the studies, divided for pathology. In this way, we hope to delineate a detailed and clear picture of the matter.

2.6. Creativity and neurodegenerative disease

Neurodegenerative diseases are a group of pathologies that share by the progressive loss of neuronal populations in specific neuronal systems as gliosis, a common pathogenesis, as insidious onset, by the progressive and inexorable decline of physical and mental condition. Based on the location of lesions in nervous system, it is possible to distinguish forms affecting the cerebral cortex, i.e. Alzheimer's Disease (AD), Pick's disease, Creutzfeldt-Jacob Disease, Fronto-Temporal Dementia (DFT), Dementia with

bodies Lewy (LBD); forms affecting basal ganglia, or Parkinson's disease (PD) and Parkinsonisms (PKS), Huntington's Disease (HD).

Depending on the type of disease, neuronal damage can cause cognitive deficits, memory issues, motor abnormalities, behavioral or psychological disorders. Neuroscience directed their interest towards studies of creativity from the observation of some of these pathologies.

The relationship between creativity and PD is controversial which. Another patient described by the same group of researchers (Bindler et al., 2011), as a result of dopaminergic therapy began to embroider napkins and developed writing skills. He began to write texts on current topics which were judged worthy of being broadcast on radio.

Other researchers documented cases of patients who excelled in visual art, so in paintings or sculptures. Walker and co-workers (Walker et al., 2006) observed a patient who had always painting skills but under dopaminergic treatment produced a large amount of pastel drawings. These drawings was appreciated for their naiveté, with a strong sense of color and kinesthetic. They were, in fact, sold in local galleries. Chatterjee et al. (Chatterjee, Hamilton and Amorapanth, 2006) examined a subject, a 68 year old graphic designer, who felt the need to paint after starting dopaminergic treatment. The patient, while drawing, reported improvements motors and felt in complete control, although in other situations felt frustration. In general he was bradikinetic, rigid, had tremors at rest and his writing was micrographic. By contrast, his artistic movements were fluid, showed an exquisite control over movements of greater amplitude. The graphics impairment was particularly evident in distal movement. The specific artistic style that he adopted showed a great breadth of the proximal movements and were relatively preserved (Chatterjee et al., 2006; Flash et al., 1992).

Even Pinker (Pinker, 2002) cited the paintings of an artist and doctor with PD, Johanne Vermette, who felt that his paintings began to improve since the disease was diagnosed two years earlier. He reported that the new style emerged was less precise but more vibrant, he felt a greater need to express himselves. Although he felt more creative onset of the disease, he believed that the drug had a role in improving the imagination.

Another interesting more recently case is the patient described by Lopez-Pousa et al. (2012) who, after the diagnosis of PD, showed an increase of compulsive pictorial production. Since he is given the dopamine agonist, and throughout the period of employment, he modified his interest in painting, which became its main activity. The patient reported that while he painted, he sensed a feeling of well-being and he felt free from mental and physical burdens of the disease. His creativity was not associated with L-dopa, but rather to the introduction of the agonist dopaminergic.

The pictorial style of the just cited patient always remained realistic. Instead, a special case described by the Japanese group led by Shimura (Shimura et al., 2012) observed a semi-professional painter with the PD, whose painting style changed radically, from abstract to realism. Some years before of developing movement disorders, psychiatric disorders, and the SNA, he began to have difficulty in painting abstract themes. He found difficult to deconstruct a realistic image and rebuild it in an abstract image. This was the very first symptom of PD. Additional evidence suggests that the first neurons affected in PD are not dopaminergic and that the SNC is involved only after the disease has been well established in other regions of the SNC (Braak et al., 2003). The special feature of this case is that the change in the patient's artistic ability occurred before the start of dopaminergic therapy and is therefore unlikely to be a side effect (Figure 1).

***Figure 1**: abstract images 1993-2008 (Shimura et al., 2012)*

Kulisevsky and his group (Kulisevsky et al., 2009) observed an amateur artist with PD who showed a decrease in interest artistic few months before diagnosis. He developed better skills after the start of therapy with a dose of levodopa of 475 mg per day. His artistic skills and his interest in the arts increased exponentially after the addition of 4

mg of cabergoline (a dopamine agonist). The painting became his only interest. After months spent to paint for the whole day, also he began to paint at night, interfering with sleep. The patient was aware of progressively disturbing nature of its activities on family relationships, but positively considered his artistic work as it was able to move more easily and felt emotionally relieved. The withdrawl of treatment with cabergoline led a rupture in the paint. The increased of levodopa, alone, was not enough to get him back to paint. It was only after the introduction of pramipexole, a dopamine agonist, that the patient began to paint, to the point where he could sell his paintings to earn. When the patient began to take 0.35 mg of pramipexole three times daily 250 mg of levodopa reached a satisfactory pictorial production without feeling the need to paint at night.

These are only a few studies, the most important, in the literature that describe the relationship between creativity and Parkinson's disease. But the PD is not the only neurodegenerative disease that showed links with the creative behavior.

For example, Miller and colleagues published a series of cases of patients with frontotemporal dementia (FTD), who had no interest in art before the illness, but with the onset of it, developed new artistic skills, however, together, to a marked deterioration in social and of their cognitive and functional state (Miller et al., 1998). Patients described created representations on the basis of their past experiences. Their art works were finely detailed and showed no abstraction signs. The authors suggested that FTD results from a degeneration of the frontal and/or temporal lobes of the brain, so the visual-constructive functions remain partially unharmed. Finally, among the clinical manifestations of FTD there are conduct’s disorders, such as perseveration, which could have facilitated creative process, encouraging continuous repetition and review of the works. In addition, another factor which may have contributed to the emergence of these new skills are the speech disorder, caused by the impairment of semantic memory.

Mell and colleagues, however, described an artist who developed progressive aphasia, probably caused by FTD (Mell et al. 2003). In this case, as the social inhibition and the artist's verbal skills were deteriorated, so her paintings became more emotional and impressionistic, therefore less detailed and realistic. With the progression of the disease, the artist began using large brushwork of bright, vivid colors. The authors hypothesized that these changes were a manifestation of the liberation from the constraints of their

training. The result was visually brilliant and evocative. Unlike patients described by Miller et all., who showed *de novo* pictorial skills, reproducing lifelike images of their past, the skills before to the artist's disease described by Mell reality is discarded in favor of more symbolic representations.

In many other cases of artists, the literature shows, however, simplification and less attention to the details. This could be a function of a different disease that different areas affects involved in the artistic production. For example, in Alzheimer's Disease (AD), a disease that causes a global cognitive decline in more advanced stages and beginning with the involvement of the temporal and parietal lobes, results in deterioration in the perception and orientation process. A series of self-portraits (Figure 2) of a British professionist, to whom diagnosed AD, is illustrative of this process (Crutch et al., 2001). Over the course of five years, combined to its cognitive decline, his works have lost of complexity and compositional balance. He abandoned the focus on the intricate details in favor of coarse brushwork and uses pencil drawings.

In this case, one could argue that the rise of abstraction was not liberation function of artistic ability but a loss of the ability to recognize the relationship between forms and structures.

It is believed that the expressionist painter Willem de Kooning was hit by AD. He shows a similar change in his art during the stages of his illness (Espinel, 1996). However, increasing abstraction is not limited to the artists with AD but it can occur in any circumstance where there is involvement of the visual pathways. Recently, Kleiner-Fisman and colleagues described the case of a professional portrait painter and illustrator of children's books who developed a corticobasal degeneration (CBD). His illness was initially detected following an abrupt change in the style of his paintings. In fact, while working on illustrations for a book of fairy tales for children, he used bright, vibrant colors and disproportionate dimensions of body’s parts of the subject, in addition to an irregular distribution of color. He has also taken several times a portrait of a young man, who finished months before, claiming that now it seemed distorted. So he tried to correct the flaws he perceived. Signs of disinhibition, neglect of the left side and perseverance (typical symptoms of his illness) were reflected in altered portrait (Figure 3). Considering that his works, before the disease, were accurate and detailed, they were realistic representations of subjects with neutral tones. His production, after

the disease, ignored completely formal conventions of a balanced composition. He used generous but not uniform quantities of color in his paintings, to the point that in some parts of the paintings appeared raised from the canvas. This was in particular in the right part of the portrait. On the left side, instead, he gave a little attention, infact is characterized by a more abstract representation of the subject.

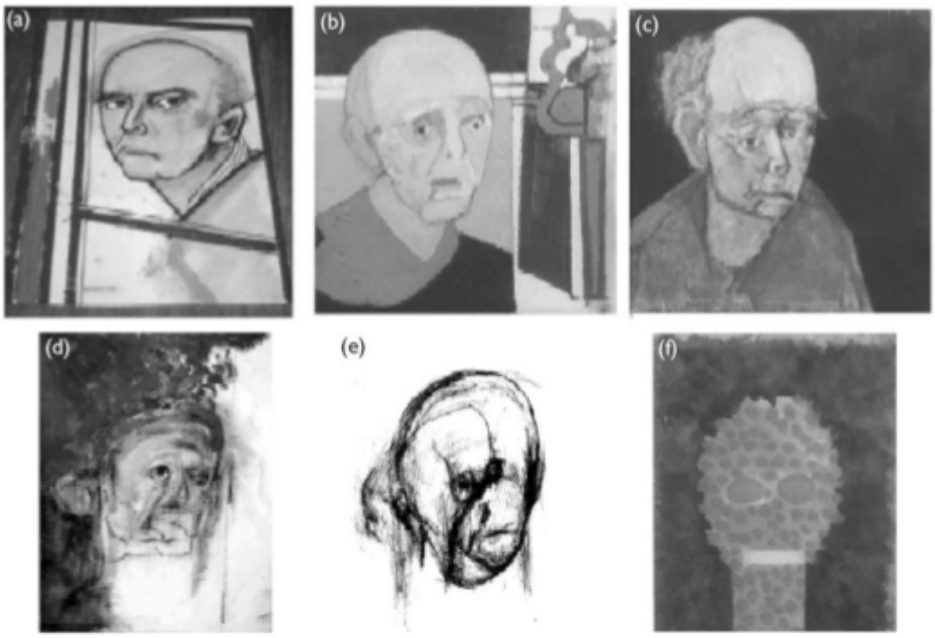


***Figure 2**: series of self-portraits of the artist suffering from AD that show the effects of disease progression on his art. (Kleiner-Fisman and Lang, 2004)*

Neuroimaging studies and neuropsychological tests detected an asymmetrical brain atrophy and dysfunction of the right part of brain. The dysfunction of right parietal lobe resulted in an impairment of visual-spatial abilities and neglect left area, while the frontal lobe dysfunction may contributed to the loss of inhibition and the maniac repetition in using of bright colors, the repetition of revisions and coarse jokes. Although in this case the abstraction is a clear sign of decline and loss of the pictorial skills. Without having to know the true nature of the painter's stylistic change, pictures are powerful and evocative. You can still claim to be art, perhaps even more if you refer to his ability to provoke an emotional response in the viewer.

***Figure 3**: paintings by an artist suffering from CBD. (Fonte: Kleiner-Fisman and Lang, 2004).*

2.7. Measuring creativity

As we have seen, Creativity is a complex and essential aspect for the understanding of human development. In 1950, J.P. Guildford, in his speech as president of the American Psychological Association, proposed to study and measure Creativity as a human intelligence factor (Piirto, 1998). Since then, different conceptions of Creativity emerged, just trying to understand the meaning of the construct. For example, psychoanalysis outlined a perspective in which personality is the main characteristic of Creativity. While the Gestalt, with Wertheimer (1945) and Duncker (1945), emphasized the problem of perception, the reorganization of the elements involved in the problem

and the process knowledge as the main key to creative behavior. Cognitive perspective, however, provides a holistic view of Creativity, which includes non-cognitive factors in creative production, personal and social ones. Moreover, Amabile (1983) emphasized the role of environment and internal motivation. It is important to underline that the adopted perspective affects the understanding of creativity.

However, despite the consensus on what Creativity appears elusive, there is no doubt that Creativity seems to reflect certain styles or personality factors. Therefore, you can consider important for Creativity personality's dimensions like having an open mind, novelty and tolerance of ambiguity as well as some cognitive functions, such as ideational fluency and flexibility of thought.

In the Sixties and Seventies were made several efforts to discover techniques to measure Creativity. It is mainly thanks to the work done by Guilford on divergent thinking that Creativity is seen as a capacity different from intelligence. From that the need to use tests to study it comes. Researches in this field are very recent. In fact, instruments available today for measurement of Creativity are few compared to other instruments that measure constructs such as intelligence or motivation.

2.7.1. TTCT

In 1974 the American psychologist Ellis Paul Torrance developed the first test to measure Creativity, known as *Torrance Test of Creative Thinking* (TTCT). The TTCT represents to date the most widely accepted tests and internationally used. The test is administered in two versions: figurative and verbal.

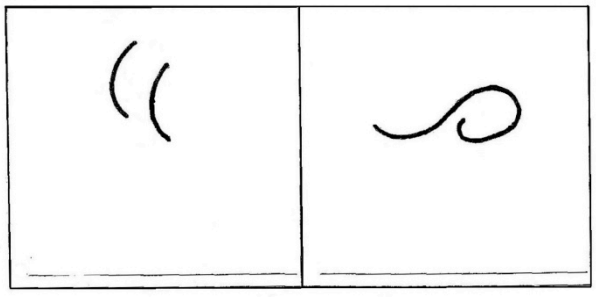


Figure 4: *examples of figurative item in TTCT.*

The figurative form uses only images. It is appropriate for both, children and adults, and takes thirty minutes. In particular, it consists of three tasks:

1. construction of drawings: a sheet of printed paper with a stimulus and starting marks is gave to the subject: the person has to draw a picture;

2. completion of images: from ten incomplete figures, the subject must build as many drawings (Figure 4);

3. parallel lines: the subject has to build designs from three pages of pairs of parallel lines (Figure 5).

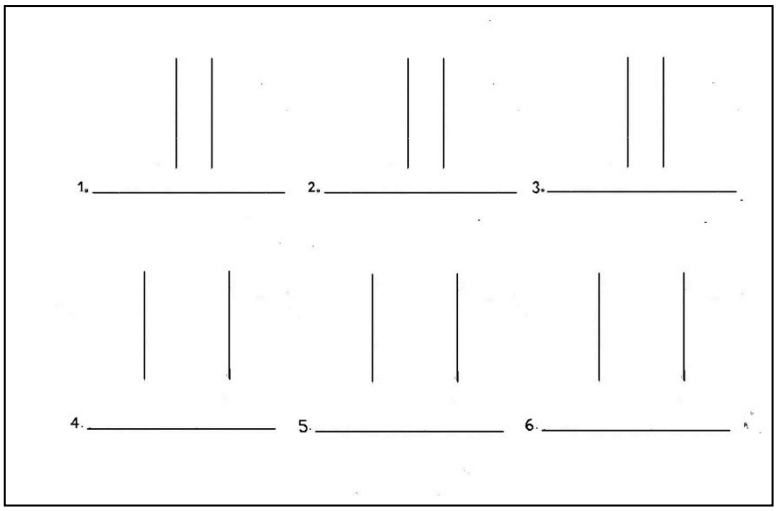


Figure 5*: parallel lines used in figurative items of TTCT*

The verb form, instead, requires a level of literacy and takes fifty minutes. It consists of five activities:

1. ask: starting from depiction of a scene, the subject must ask questions;

2. interpret: with the previous depiction, the subject must interpret possible causes and consequences of the representation;

3. perfecting of a product: the person must indicate possible ways to improve the use of a toy in order to make it more fun;

4. unusual uses: the subject has to offer unusual use of a product;

5. suppositions: the subject require to list assumptions of the consequences of an unlikely situation.

The tests are designed to measure four mental characteristics:

a) *fluidity*, as the ability to give more possible solutions to a problem in a reasonable but limited time;

b) *flexibility*, as the ability to develop solutions from different components and multiple perspectives, and to quickly change perspective and frames of reference;

c) *originality*, as the ability to develop statistically improbable ideas. It means venturing into creative spaces not yet crossed by anyone, looking for new and effective solutions;

d) *elaboration*, which refers to having attention to detail and respect for their work, and

to present a consistent product: it is finished in all its parts, impeccable both in substance and in form, taking the time necessary for the verifications but on time to be delivered.

To summarize, the TTCT measures the ability to provide many answers (fluidity), not discounted (originality), inspired by different elements (flexibility), and providing a good level of detail (processing). The intuition behind the TTCT is commonly shared: who does any creative work should discreetly get by in all four areas, and it should be excellent at least in one, and maybe more than in one.

2.7.2. ATTA

In the experimental field is widely used administration of the shortened version of the Test of Torrance (*Abbreviated Torrance Test for Adults* - ATTA in Goff and Torrance, 2012). It is composed of three activities:

1. a verbal task: tester presents to the subject an unlikely situation and he asks to make the greatest number of assumptions and suppositions if this situation were to actually occur;
2. a first visuospatial task: from a sheet with already designed a stimulus, the subject must create a representation, giving a title and a meaning;
3. a second visuospatial task: tester tell the person to do as many possible designs from nine pairs of parallel lines.

Each drawing will have a meaning and a title. The subject has five minutes for each activity, for a total of fifteen minutes.

The dell'ATTA assessment is the same as in the full version.

2.7.3. Wallach-Kogan creativity test

Another fairly used reagent is the Test of Wallach and Kogan (1965, cit. In Antonietti, 1990). According to Wallach and Kogan, we can be defined that creative individuals are characterized by a hierarchy of "wide" responses, so they can produce, in association trials, a greater number of responses, including many rare or unique responses. Equipped with less creative potential individuals are instead the subjects characterized by a hierarchy of "steep" responses, which produce few associations and for most stereotyped. The Wallach and Kogan's test includes both verbal and non-verbal mental trials using pictures.

The test takes some materials developed by Guilford. In addition, the authors emphasize the importance of an atmosphere of play rather than examination and the abolition of time limits in the tests in order to get real information on the Creativity of the participants. The lack of time and the rigid structure of a context judges do not seem to favor a divergent production.

2.7.4. TCD

Williams (1994) created the test of Creativity and divergent thinking (TCD) which consists of two different instruments: the test of divergent thinking and the test of the creative personality. This test reveals a combination of features which contributes to the creative process, the creative personality and creative product.

A third tool, Williams' scale, is an assessment protocol for parents and teachers of children who received the first test.

The test of divergent thinking measures a combination of verbal skills which depend on the left hemisphere of the brain, and visual-perceptual skills which depend on the right one. The test gives scores for the four factors of divergent thinking: fluency, flexibility, originality, elaboration. The processes are evaluated according the divergent transformations of figures and awarding them titles, requiring verbal skills and is defined divergent semantic transformation.

The Test of the creative personality is a list of 50 items of multiple choice, in which subjects are asked to think of as being curious, imaginative, attracted by the complexity, likely to accept risks and gives scores on the emotional aspects of nature: curiosity, imagination , complexity, willingness to take risks.

The Williams' scale is a scale which indicates the degree to which each factor is owned by the observed child and it can also serve for assessing the abilities of his parent or his teacher.

2.7.5. Infant Creativity Test

The newly designed *Test of Infant Creativity* (TCI) of Cerioli and Antonietti (1992) measures the creative potential of children. According to the authors' evidence, they trigger mental codes, both visual-figural base both verbal base. The TCI is designed to be used in schools. For this purpose it was necessary to take into account the following constraints:

a) simplicity, so that it can also be given by persons whose training in this regard should not be overly intense and prolonged in time, and without requiring special environmental situations;
b) for sake of brevity, to ensure the possibility of use even on large samples and in the respect of the normal time of school activity;
c) uniqueness of administration and scoring procedures, to standardize, through compliance with the specification although flexible, detection and data evaluation criteria.

The TCI includes trials to evaluate the fluidity, flexibility and originality in spontaneous production of tasks from visual or auditory stimuli. Other trials instead evaluate intellectual abilities, creative ones with more complex tasks. It consists of two identical versions, each one consists of 6 trials:

1. Examples (3 items): the child has the task of numbering as many as possible of fact having a given property;
2. Drawings (3 items): the child is asked to list the possible meanings of a graphic pattern;
3. Use (item 3): the child is requested to list as many possible uses of a given object;
4. Consequences (2 items): the child is asked to list the possible consequences of bizarre and fantastic events;
5. Stories (2 items): it urges the child to invent a story from a graphic illustration;
6. Problems (2 items): tester presents a simple problem of a practical nature and the child has to propose possible solutions.

As the numerous applications of the TCI, the test, proposed according to a playful mode, is easy to administer as it is fairly short despite having no time limits.

2.7.6. Remote Association Test

In 1962 Mednick created the *Remote Association Test* (RAT), modeled on the basis of the main tests of intelligence (Sternberg & O'Hara, 1999). Mednick postulated that any ability or tendency to produce remote ideas facilitates creative solution. The author used the "associative hierarchy" term to indicate the frequency of the usual answers and those unusual dates in association tasks. Faced with a problem, the subject of research gives usually combinations of answers belonging to the given criteria. For example,

standing in front of the word, most people will associate the word “shoe”, and this would be, according Mednick, a little creative response. A truly creative response would associate with the word foot, the word soldier. The RAT provides a series of three words and the candidate must find a fourth that links to the previous one, forming a new and creative association. There are various levels of difficulty, for example:

Electric high-wheel (chair)

Swiss cottage pie (cheese)

Political line surprise (party)

House shoe palm (tree).

3. PARKINSON'S DISEASE

3.1. Parkinson's Disease: definition

Parkinson's Disease (PD) was described for the first time by James Parkinson in a booklet entitled "Treaty on the Shaking Palsy" published in 1817.
Shaking palsy is the name that identified the disease for nearly a century until it was realized that the termination proved inappropriate because Parkinson's patients are not paralyzed. It thus began to use the term idiopathic parkinsonism, but the correct term is "Parkinson's Disease", which also honors the physician who first described it.
But what is Parkinson's Disease?
PD is a movement disorder of unknown cause provoked by an imbalance of neurotransmitters in the basal ganglia. The average age of onset is around 60 years, but there are also a youthful beginnings.

3.2. Structures and circuits

The PD is characterized, from a neuropathological point of view, by the progressive degeneration of selective neuronal population, which includes the dopaminergic neurons of the substantia nigra of the midbrain.
Dopamine is a neurotransmitter that belongs, together with noradrenaline (NA) and adrenaline, to the category of catecholamines. The catecholaminergic neurons are present in regions of the nervous system involved in the regulation of the movement, mood, attention and visceral functions. In particular, dopamine plays an important role in behavior, cognition, voluntary movement, motivation, punishment and satisfaction, sleep, mood, attention, working memory and learning. Also it acts on the sympathetic nervous system, causing increased heart rate and high blood pressure. The dopaminergic neurons are present mainly in the midbrain, in the substantia nigra, and hypothalamus.
The substantia nigra of the midbrain is the area where concentrates more neuronal loss (Figure 2). This nerve structure is the home base of the nigrostriatal dopaminergic pathway (Figure 1). Dopamine, released at the level of the *striatum*, modulates neuronal circuit activity of the *basal ganglia* that allows adjustment and learning of motor skills, as well as some essential cognitive functions. The degeneration of the nigrostriatal pathway leads to dysregulation control the activity of the basal ganglia motor activity

and the appearance of the classic symptoms of the disease: bradykinesia, muscle hypertonicity and resting tremor.

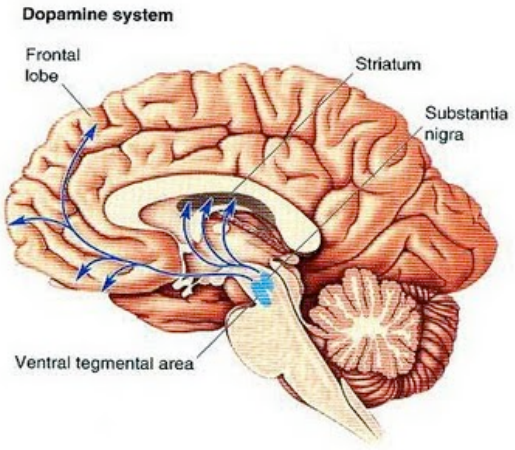


***Figure 1**: dopaminergic system that originate in the substantia nigra and ventral tegmental area (Bear, Connors & Paradiso)*

In the neurodegenerative process, they are also involved cholinergic basal *nucleus of Meynert*, which provides cholinergic input to the cerebral cortex, to hypothalamic neurons, to cortical neurons as well as to whom in the olfactory bulb and in the ganglia of sympathetic and parasympathetic intestinal (Antonini & Barone, 2008): the degeneration of these neuronal structures is responsible for the non-motors symptoms of the disease.

Changes in subcortical structures such as the basal *nucleus of Meynert*, the *locus coeruleus* and the *raphe nuclei*, resulting in the appearance of cognitive symptoms of the disease, mainly of attentional deficits and executive function (Chaudhuri, et al. 2006).

The involvement of serotonergic pathways can be considered the basis of depressive disorders that often appear in the course of the disease.

The changes of the olfactory bulb cause anosmia and degeneration of the intermediate-lateral columns of the spinal cord, the sympathetic and parasympathetic ganglia and the central nucleus of the amygdala that cause autonomic dysfunction.

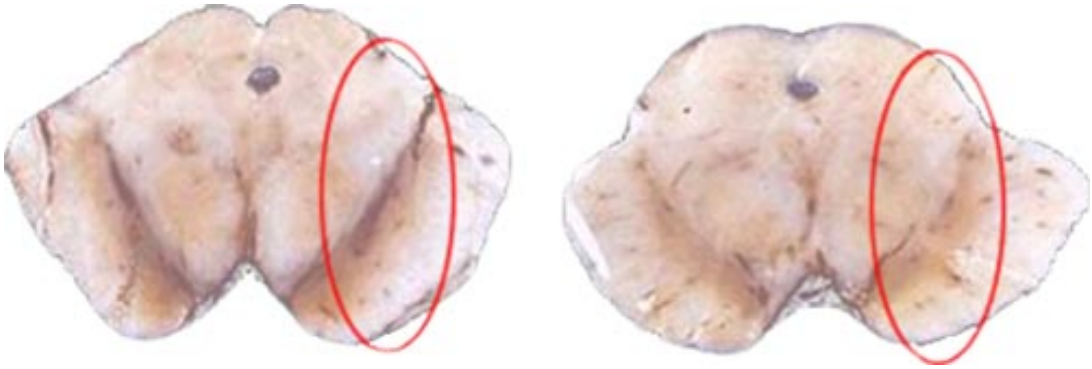


Figure 2: *comparison between the midbrain's substantia nigra in healthy subject (left) and PD patient (right).*

In addition to the degeneration of neurons groups present in certain structures, at the neuronal level, there is the appearance of Lewy body: these are abnormal protein aggregates which develop inside nerve cells.

However, Lewy bodies may or may not represent a specific element of the Parkinson's Disease since they are also present in other neurodegenerative diseases. Is noteworthy, however, the fact that it was found a prevalence of age-specifc Lewy bodies in the brains of people without clinical evidence of Parkinson's disease: this suggests to us that, probably, their presence indicates a presymptomatic stage of the disease (Antonini & Barone, 2008).

The actual duration of the preclinical phase, the period between the beginning of the pathological changes in the substantia nigra and the onset of the symptoms of Parkinson's disease, is controversial: several studies speak of a long prodromal of several decades, the post-mortem data and PET studies have identified a latency period of about five years (Antonini & Barone, 2008).

3.3. Etiology

James Parkinson first described the disease which he called *shaking palsy*. Many tried to describe it and find a cause, but without success. The disease is called *idiopathic*, from *idios*, himself, and *pathos*, suffering: is an adjective used primarily in medicine that indicates an illness not due to external causes or notes with no apparent cause, or primitive; it means approximately "a disease of its kind".

Charcot gave guilt stress, others saw it as an endocrine deficit and other hereditary disease. Last researchs attribute the cause of this disease to a combination of factors: exposure to toxic substances and genetic predisposition would play a key role.

This etiological hypothesis is supported by a group of young Californians with PD who in 1984 noted how the disease had began subtly. All they reported to be addicted and having taken a particular drug called *new heroin*. This substance was then classified and renamed MPTP, a tetrahydropyridine. One can only say that MPTP like substances act as toxins, causing necrosis of the neurons of the substantia nigra and the subsequent onset of symptoms (Langston & Ballard, 1984).

Recent genetic and molecular studies have revealed some rare forms of PD characterized by the transmission of a defective gene in autosomal dominant form (-*Y Nuclein*) and recessive (*parkin*). In these forms it remains clearly a complex interaction between genetic and non-genetic factors (Peppe, 2009).

Other studies, however, have investigated the influence of tobacco, coffee, alcohol, and dietary factors. It was discovered that both exogenous and endogenous substances have the potential to damage the nigrostriatal neurons and consequently induce PD, however, their precise role remains uncertain.

What is known for sure is that in the majority of patients, especially those with a negative family history, the disease is caused by a complex interaction between a particular genetic predisposition inherited within the family and several environmental factors to which the patient is exposed during in their life (toxic substances, drugs, lifestyle, etc.), which interact differently with each other up to the outbreak of the disease.

However, the typical symptoms of the disease would appear when there is a reduction of the amount of dopamine in the striatum (Figure 2) of at least 80% (Bernheimer, 1973).

3.4. Set of symptoms

The major symptomatic manifestations of PD are bradykinesia, tremor at rest and rigidity. They are directly related to the decrease of dopamine in the striatum (caudate nucleus and putamen, which are the basal ganglia: figure 3).

But there are other symptomatic manifestations, less known, including sensory symptoms such as pain and excitement, hyposmia, sleep disturbances, depression, anxiety and finally to executive function and working memory deficits. The clinical manifestations of PD are a complex interaction between the intrinsic characteristics of

the disease, side effects to drugs, environmental factors, genetic and related to aging (Rodriguez-Oroz et al., 2009).

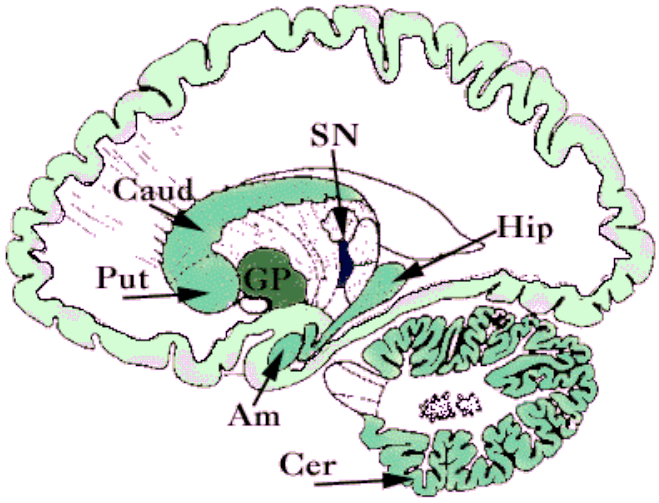


Figure 3: *Basal Ganglia, Putamen; Caudate and Globus Pallidus (ACT, 2015)*

3.4.1. Motor symptoms

The motor manifestations of PD begin focally, typically in a body segment, when the dopaminergic concentration levels drop below 80%.

The main motor symptom is *bradykinesia*, a neurological disorder characterized by the difficulty of the motion to start a new movement, and slow implementation of the same and manifests itself in 77-98% of cases. Typical events are the reduction of the frequency of eyelid movement, facial expression and reduced absent or reduced movement of arms while driving (Rodriguez-Oroz et al., 2009).

Although all types of movements undergo a slowdown in the PD, empirical evidence shows that the activated from the outside movements are less compromises with respect to the patient's voluntary movements (Morris et al., 1996).

In advanced stages of the disease, bradykinesia can disrupt daily activities such as getting up from his chair, brushing and move in bed. We also observe hypomimia, ie a reduction of facial expressions, hypophonia, the voice becomes weaker and weaker and the micrograph (Figure 4), the writing becomes more and more small and uncertain (Peppe, 2009).

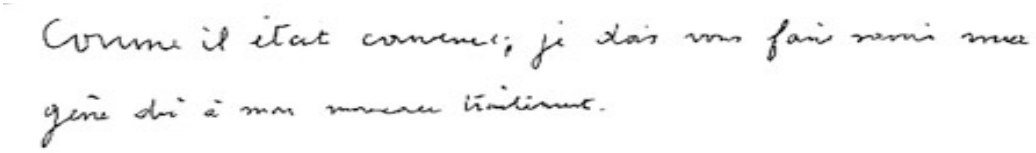


***Figure 4**: Example of micrograph in a PD patient (Ferri-de-Barros, 2011)*

Tremor is one of the initial symptoms of the disease and is a sign of benignity of the disease. An onset of rigid-bradikinetic type, with slowing and rigidity, is a negative progression factor (Zetusky et al., 1985; Hershey et al., 1991).

The tremors are involuntary movements, oscillators and rhythmic of one or more parts of the body with respect to an axis of equilibrium. Their nature is often pathological and are caused by the alternating contraction of muscle groups that are opposite to each other. You can make a classification of tremors going to consider the mode of onset, the frequency of oscillation, as the movement appears wider, taking medication, and the coexistence of neurological diseases (Figure 5).

***Figure 5**: Proof that is performed during the neurolical examination for evaluation of tremor (International Essential Tremor Foundation, 2015)*

Depending on the circumstances in which it appears the tremor may be: at rest or in action. Tremor at rest is typical of Parkinson's Disease and is maximum to the state of total limb rest. It is at low frequency and is regular. It stops when the subject begins a movement.

The action's tremor is instead caused by a muscle contraction that appears during a voluntary movement or when it is maintaining a fixed position. Usually it disappears when the limb returns to a rest position.

The tremor can be further divided into physiological or pathological. It is physiological when it appears in maintaining a fixed position for a long period of time and is typical of healthy people. It is short and can be amplified by stress, cold, caffeine or the presence of fever. The pathological tremor can appear as a result of various diseases

such as stroke, multiple sclerosis, metabolic disorders or trauma. Different from others tremor is what is known like essential tremor (ET) that affects about 6% of the population, especially the elderly. It is a tremor that mainly concerns the arts and the causes are not yet known. It is believed that environmental factors play a decisive role, together with genetic factors (International Essential Tremor Foundation, 2015).

The tremor in PD, is manifested at an average frequency of 3-6 Hz and is present in about 70% of parkinsonian patients. The fingers are the main affected, giving rise to the classic "Pill rolling movement." This movement is characterized by finger flexion-extension in combination with abdo-adduction of the thumb and it is as if the person was rolling a ball in his hands or counting coins.

Tremor initially affects the upper limbs and then spread to the lower and is usually unilateral. In more advanced stages also it spreads to the contralateral side, while maintaining a certain asymmetry (Peppe, 2009). The muscles of the jaw and tongue may occasionally be involved, while the abdominal muscles, back and neck are rare. The tremor may increase in stressful situations and is reduced when the patient should start a movement, when is in a situation of calm and during sleep. The typical PD tremor, rest's one, rarely interfere with daily activities, while a action's tremor, which can nonetheless be included in the PD, can seriously interfere with work activities that take advantage of fine motor skills. Another type of tremor which refer patients is defined internal tremor, a sensation felt internally but not externally; it is part of a series of annoying symptoms, non-hazardous, which are affected in inconstant way of therapy (Pezzoli, 2003).

The rigidity is present in approximately 89% of patients with PD and is caused by increased muscle tone. It may occur to palpation's tests carried out on neurological assessment that may show that the patient has a reduced muscle distention following passive movements and presents a resistance to stretching. Rigidity, together with bradykinesia, helps to determine the overall degree of patient disability (Rodriguez-Oroz, 2009). As with the tremor, rigidity also often has a unilateral onset, can range throughout the day and is influenced by stress and emotions. The initial involvement of a limb can occur especially with pain, which can lead to incorrect diagnosis of arthritis or bursitis.

Contrary to the other three cardinal signs of PD, postural instability occurs late in the course of the disease, typically after ten or more years since its inception, and is undoubtedly the least favorable symptom because is poorly responsive to drug therapy (Pezzoli, 2009). The early onset of postural instability should prompt the clinician to suspect an atypical parkinsonism. The postural instability is mainly due to a reduction of righting reflexes for which the patient is not able to automatically correct any variations of balance. The balance is controlled in fact by the extrapyramidal motor system that receives input from the visual system, vestibular and proprioceptive; these sensory afferents are integrated to compose the body scheme. When the patient is stopped, the image on the retina is stable, however, when the patient moves originate of the typical mechanisms of adaptation of the pathology for which a wrong position is perceived as perfect (Schieppati et al., 1994; Horns et al. , 2003). This type of mechanism is also at the origin of another noise typical of PD, the phenomenon of the Tower of Pisa: the patient takes a wrong position by tilting the torso to the right or left, without noticing.

The postural instability associated with gait disturbances often proves to be the most disabling manifestation and less treatable of the disease. The first sign of a gait disorder is reducing the oscillation of the limbs, but over time patients begin to walk in small steps, uncertain and shuffling. The beginning of the walk and turn around become especially difficult. The loss of postural reflexes and kyphotic posture can lead to a festination (from the Latin: *festinare*, hurry).

Finally, a typical symptom of the most advanced stages of the disease is the *Freezing of the Gait* (FOG) which covers approximately 30% of patients with PD (Giladi et al., 2001). The term describes the inability of starting off and stopping it when the attention is called by a stimulus, when you have to change direction and when driving through narrow passages. The patient claims to feel that your feet are glued to the floor (Peppe, 2009). FOG episodes have been associated with other deficit of the gait such as the slowness and the asymmetry of the way and even shorter steps (Cowie et al., 2005). It's interesting to note that these abnormalities in the walk tend to occur during the tasks walk on command, which require a high level programming such as turning on themselves, move between very narrow openings and avoid sudden obstacles (Snijders et al ., 2008). Recent studies have suggested that the areas involved in attention control

and programming, play an important role in the gait. Patients with PD are more susceptible to the influence of a secondary cognitive task while they are facing an obstacle in their path; this task could further slow the walk (Hausdorff et al., 2003). The freezing may also affect other parts of the body such as the voice. Furthermore, in some cases we observe the opposite phenomenon: the paradoxical festination (sudden release of the gait for which patients perform very short steps and close without being able to stop, causing frequent falls).

Many times patients complain of pain, dystonia, feeling of pins and needles, or the perception that the limb is asleep. Dystonia is a syndrome characterized by prolonged muscle contractions that cause twisting movements and abnormal postures. The dystonic movements are slow and involve the limbs and trunk; by some authors they were compared to the twist of a screw. The latter may frighten the patient, but you must remember that this is not a dangerous condition.

3.4.2. Non-motor symptoms

The scientific knowledge's improvement on the pathophysiology of PD, led to increased clinicians attention to the presence of non-motor symptoms, which are among the major determinants of the quality of life of people with PD.

The degenerative process responsible for the PD develops in stages and it gradually affects different nerve structures in ascending order. Therefore, as the disease progresses, the vegetative disturbances become to be increasingly frequent, if not constant.

There are symptoms of vocal type: the voice is weak and loses the tones so that the patient speaks in a rather monotonous. Another feature of PD patient's speech is the tendency to accelerate emission of sounds and to start to thicken (Peppe, 2009). In other cases it may be frequently a kind of freezing of the word, thus it generates a stuttering problem. All this may compromise the patient's chances of being understood.

The problems associated with swallowing may occur at an advanced stage of the disease due to a lack of coordination of the muscles of mastication, phonation and swallowing. When the coordination between these muscles is not correct, the patient may have the unpleasant feeling that the food stopped in the throat and frequently it resorts to coughing fits to resolve the situation. This difficulty may occur with both liquids with solids, but it refers more often to liquids (Pezzoli, 2009). Related to the previous

problem is the excessive presence of saliva in the mouth, causing a very annoying symptom for the patient: the *sialorrhoea*. The loss of saliva is linked to a reduced swallowing and not to an increase of the saliva produced.

In recent years awareness of the importance of clinical sleep disorders of PD increased. Perhaps they shared by other non-motor disorders typical of the advanced stages, such as psychiatric and cognitive behavior to high ecological impact on personal and family health and their organization in general. Among the non-motor symptoms, sleep disorders certainly play a very important role for their frequency. They are indicative of possible co-morbid conditions and they often are accentuated with the aggravation of disease conditions contributing to the deterioration of patient and family members' quality of life (Adler & Thorpy, 2005).

The prevalence of sleep disorders, including in their generality, varies from 40% to 90%. Some REM parasomnias, such as REM sleep behavior disorder (RBD), sometimes precede by years the onset of motor symptoms and they are currently interpreted as diagnostic predictors (Schenck at al. 1996).

Sleep in Parkinson's Disease is altered not only in terms of quantity (insomnia, excessive daytime sleepiness) but also quality (parasomnias). Table 1 shows a classification of sleep disorders most frequently encountered by patients with PD.

Motor disorders related to the disease	Difficulty falling asleep can depend on nocturnal akinesia which prevents the patient to move in bed with agility.
Restless Legs Syndrome (RLS)	RLS is a sensory motor disorder related to sleep and it is characterized by a strange feeling of "discomfort" in the legs, associated with a strong desire to move them.
Anxiety-depression disorder	Depression is a common cause of sleep's alteration at night, resulting in early morning awakening, fragmentation of sleep and reduced REM latency.
Urinary problems	In PD, especially at an advanced stage, frequent urination is the leading cause of nocturnal awakening and is a very common disorder among patients.
Obstructive Sleep Apnea Syndrome (OSAS)	Obstructive sleep apnea, central apnea and episodes

	of hypoventilation.
Periodic Limb Movements (PLMs)	Periodic limb movements are movements of dorsiflexion of the foot on the leg and sometimes the leg on the thigh that are repeated regularly (every 20-30 seconds) they are often followed by awakenings or lightening of sleep.
Vivid dreams, nightmares	It can happen that dreams are so intense and real as to seem almost real. Often dream content is violent and distressing for the patient, who tends to wake up. In some cases the reality's feeling of dream is so strong that the person upon awakening can see images of dream. These visual hallucinations are transient and may disappear as the light.
Rapid Eye Movement (REM) *Sleep Behaviour Disorder* (RBD)	The RBD is a REM parasomnia characterized by sudden movements, especially of aggression and defense, somniloquio and shouts, as if subjects themselves interacting with prorpio dream.
Talking in sleep	The patient can speak with articulation of sentences, or sometimes unintelligible shouts, screams, cries or laughs. It can be accompanied by a fine gesture or coarser.
Confusional aweking	States of nocturnal confusion, characterized by personal disorientation in time and space, are typical of the advanced stages and are largely associated with global cognitive impairment.

Table 1: *The most common sleep disorders in PD.*

3.5. Psychiatric manifestations

Among patients not medically treated, at the early stages of the disease, 37% shows depression, 27% presents a apathetic picture, 18% suffering sleep disorders and 17% of anxiety disorders (Aarsland, 2009). These disorders may fall after taking dopamine agonists, treatment of choice for Parkinson's Disease (Menza et al., 1993). Depression appears in approximately 50% of patients during clinical course, although it is often underdiagnosed (Reijinders, 2008).

Literature's data on the prevalence of depression in PD are characterized by extreme variability which depends on the difficulty in defining the depression itself, in a disease where a part overlaps with the symptoms of depressive symptomatology. In fact, the

psychomotor retardation, the decrease of the initiative and the lack of interest in life's activities which characterize depression are confused with bradykinesia.

The depression in PD has not of exogenous origin, which is reactive to the diagnosis of a chronic disabling disease, but it has a biochemical basis, being likely the result of the damage of the serotoninergic neurotransmitter (Sano et al. 1990) and the involvement of noradrenergic and dopaminergic limbic structures.

The clinical profile of depression in PD is characterized by a high incidence of dysphoria, irritability, pessimism for the future. However, comparing to depressed patients without Parkinson's Disease, there is a reduced frequency of guilt, dysthymia, feeling of failure and suicide (despite the high suicidal ideation).

Many PD patients with depressive symptoms, however, do not meet the diagnostic criteria for major depression or minor depression proposed by the DSM IV-TR, despite having, however, these symptoms clinical relevance. That condition was called subsyndromal or subthreshold depression (Judd et al. 1994). Patients present with two or more depressive symptoms below the threshold level, which indicates a brief presence of symptoms. The anxiety disorder is the second most common affective disorder in PD patients, being found in about 40% of patients. Its main features are the sense of worry, fear or apprehension. The diagnosis of PD may precede up to twenty years and it constitutes a risk factor.

However it is often difficult to discern symptoms of anxiety than depression. Because, even with them, there are associated symptoms of autonomic type, somatic, emotional and cognitive development which are part of the PD phenomenology, making diagnosis difficult. Moreover, anxiety disorder may often have a variable trend, being associated with the on-off motor fluctuations, associated with off stage in 66% of cases and correlates with high disability (Menza et al. 1993).

In conclusion, affective disorders in Parkinson's disease is a common complication and often underestimated which undermines the quality of patient's life. Often depression and anxiety disorder precede by several years the onset of parkinsonism.

Another psychiatric symptoms that PD patients may suffer is the Impulse Control Disorder (ICD). This disorder is characterized by the inability to resist the impulse to implement self-destructive behaviors or behaviors which may cause long-term negative consequences (Grant et al., 2005). People with this disorder feels a lot of tension when

they want to put in place a certain behavior, and when we find it,they feel a sense of great pleasure which lasts but for a short time (Adam et al., 2008). However, this condition seems closely linked with dopaminergic therapy (Canesi et al., 2012). The DSM-5 describes various forms that the ICD can take: explosive anger, kleptomania (or the urgency to steal objects of any kind), trichotillomania, pyromania, compulsive shopping, binge eating, hypersexuality and gambling.

3.6. Cognitive profile

Some authors like Ferrer (2009) highlighted involvement of cortical structures during the progression of PD which determines changes in affective and cognitive spheres. According to the Society of the Movement Disorders (MDS), 26.7% of PD patients develops a *mild cognitive impairment* (MCI or *Mild Cognitive Decline*) (Litvan et al., 2011) and 40% develop dementia (PDD) (Goetz et al., 2008). According to the latest research would be 83% of PD patients develop dementia (Hely et al., 2008).

Originally the Parkinson's disease was considered only a movement disorder which did not involve a cognitive involvement. The research of recent years have instead shown that cognitive impairment is one of the characteristic elements of the disease: patients can present a dysexecutive syndrome, mnemonic and visual-spatial deficits (Dancis et al., 2015).

Typical neuropsychological disorders of Parkinson's Disease occur mainly as frontal deficits and subsequently it may affect more posterior cortical regions.

It is believed that executive functions are more involved in the early stages as the ability to plan, executive control, flexibility, organization and ability to set-shifting (Dubois and Pillon, 1997). Recent studies by Green et al. (2002), Janvin et al. (2003) and Muslimovic et al. (2005) have shown that deficits of this type concern the majority of the Parkinsonian population without dementia and that these disesecutives disorders become more severe with the progression of the disease.

The working memory deficits are fully included in the neuropsychological framework of the disease. Baddeley (1992) described working memory as a "Cognitive function that provides storage and manipulation of information necessary for complex tasks such as language, understanding, learning and reasoning". Considering the empirical evidence of working, memory deficits can be attributed to the executive nature deficit,

which compromises patient's ability by using attentional resources and on-line monitoring stored material (Brown and Marsden, 1991; Wu and Hallett, 2008).

The long-term memory disorders are equally present in PD patients without dementia. Patients have specific difficulties in the free-recall tasks where they have to freely recall at memory information previously stored. Probably, as suggested by some authors as Taylor (1990) and Vriezen (1990), success in free recall tasks depends on the use of effective strategies in the encoding and recall. Patients with PD in fact show a clear improvement in recognition tasks.

Some recent research suggests that the prospective memory is particularly impaired in PD patients. It is considered the ability to remember to perform an action in the future if a specific event, or upon expiry of predetermined time. It is believed that this component of memory is closely linked to executive functions (Einstein & Daniel, 1996). Some activities that may be impaired in patients with deficits in prospective memory is such an important event to remember or follow a work project, but also remember to take the therapy. Deficits of this type have inevitably relapse work and social activity.

"Dementia is a syndrome characterized by a progressive cognitive decline of cognitive functions which are associated with behavioral disorders and psychopathological manifestations" (Grossi & Trojano 2002). The most common form of dementia studied and understood is Alzheimer's Disease (AD): a degenerative disease which involves the whole cortex starting from the temporo-parietal areas. However, recent research identified other forms of primary dementia differ from AD (Neary & Snowden, 1996).

In the forms of degenerative dementia different from AD, degeneration initially affects prefrontal areas with subsequent impairment of subcortical areas. These forms are characterized by behavioral disorders which have an impact in the daily life and early deficits of executive functions; these last is present in AD only in the late phases (Duke & Kaskniak, 2000). In Parkinson's disease there is a substantial reduction of dopaminergic neurons in the striatum. Dopamine plays a central role in kick off and inhibit movements but not only: it plays a fundamental role in cognitive processes (Buttaro et al., 2013).

The exact mechanism underlying the cognitive impairment is not yet known. It is known however that in a large majority of patients with PD there is a diffuse brain

atrophy. Neuronal necrosis in patients who develop Parkinson's Dementia (PDD) is largely attributed to the presence of Lewy bodies in the cortex, which are deposited on the neurons and damage them up to take them to death (Pfeiffer, 2012). The Lewy bodies can also be found in Lewy body dementia (LBD) although in this form the cognitive degenerative changes already appear in the debut stages. At the moment there is still no agreement within the scientific community whether LBD and PDD are two distinct forms, or the evolution of the same disease (Aarsland, 2012). According to the Queen Square Brain Bank criteria for the diagnosis of PDD must coexist a picture of PD and dementia framework. In addition to typical symptoms such as bradykinesia, resting tremor, rigidity and postural instability there must be an impairment in at least two cognitive domains of memory, language, visual-spatial and executive functions. Even dementia by Lewy bodies is characterized by tremor, rigidity and cognitive impoverishment; therefore idiotic symptoms related to PD must appear at least a year away from the motor symptoms. (Goetz, 2008). Some authors tried to identify the possible risk factors to predict with a good chance if the Parkinson's disease will have a relapse in dementia. Horoupian and co-workers (1984) and Hofman (1989) identified as major risk factors family history of dementia and age of disease onset. Marder (1994) considered as a risk factor in the severity of extrapyramidal symptoms debut, Lewis (2005) speaks of the presence of mild cognitive deficits. While Janvin (2006) considers the presence of post-administration mental confusion and psychotic symptoms of Levodopa the major risk factors for the development of PDD. In the early stages dementia related to PD, compared to the AD, it is characterized by a greater involvement of attentional and executive functions, less impairment in the recognition tests and fewer decay of long-term memory semantics. The aphasic disorders, agnosia and apraxia, are much more rare, while we find most frequently anxiety disorders, depression, hallucinations and pronounced apathy (Emre, 2003; Caballol et al., 2007; Emre et al., 2007). Despite overall PDD generally are no aphasic disorders, verbal fluency deficits and alterations of name (especially verbs) can appear (Dubois & Pillon, 1997). Some research observed a positive correlation between the presence of depression and the onset of cognitive deficits in PD. They argued that cognitive decline is so rapid in PD patients with a marked depressive symptoms. Depression in Parkinson-Dementia complex is associated with a reduced functioning of the

orbitofrontal circuit for the decrease of dopaminergic projections from the aera ventral tegmental area (Cummings, 1993). Other authors instead explain the presence of depression in the PDD as an impairment of the anterior cingulate cortex (Ring et al., 1994). Hallucinations and psychotic symptoms often appear in patients with auditory and tactile dementia, ften threatening content (Barnes & David, 2001). The presence of hallucinations could be attributed to a reduced frontal operation, with failure inhibition (Grossi et al., 2005). Delusions are less frequent and they are often characterized by persecutory ideas. Dementia in PD is characterized by a neuropsychological framework similar to other subcortical dementias, with a greater involvement of the visual-spatial functions. The parkinsonian patients make errors in the tasks of copying image and writing tasks, which need to integrate various spatial information (Barbarulo & Grossi, 2005).

3.7. Drug treatment

Therapy in a PD's patient is time to recover the best motor function. The current therapeutic remedies are able to correct symptoms but not cure the disease permanently, which is why it is important that therapy includes both pharmacological treatments that do not, such as physical therapy and psychotherapy.

The fundamental cure for PD is through the administration of the chemical compound *L-DOPA* (*L-dihydroxyphenylalanine*), a precursor of dopamine. The L-dopa crosses blood-brain barrier and increases synthesis of dopamine in the *substantia nigra* cells, thereby alleviating some symptoms. The allocation of symptomatic drugs currently available is wide: today, you can set up an effective and safe therapy from the initial stage of the disease, personalizing the treatment in relation to the clinical picture and the demographic and social characteristics of the patient.

Clinical experience up to now accumulated and the results of experimental studies have shown that the real therapeutic challenge in the management of advanced disease is when they appear motor complications (Antonini & Barone, 2008). For this reason, the choice of initial therapy of a de novo patient must take into account not only the control of current symptoms, but also the possible development of motor complications, which must be prevented and / or minimized by choosing the appropriate therapeutic strategy, in light of scientific knowledge.

In addition, the life expectancy of a patient who is ill with PD today is comparable to which of a healthy peer, therefore the therapeutic strategy should be planned in view of a lapse of many years of illness.
In the choice of drug to be used at the beginning of the treatment, it is important to thoroughly know the individual characteristics of the patient, especially age, his general health and the type of work, social relationship and family.

3.7.1. Levodopa

Known since the early 60's, levodopa, converted into dopamine in the central nervous system (CNS), is still considered the most effective and easy to handle medication in the PD treatment. The pharmacological response to levodopa is represented by two answers. The short answer is characterized by an improvement in symptoms which can last from minutes to hours after taking a single dose of levodopa. The long-term answer is characterized by an improvement in symptoms after days of starting therapy and a beneficial effect from being exhausted in a equally long bow, once suspended therapy (Zappia et al., 1997). Therapy has many limitations and one of the main one is the so-called *syndrome treatment with levodopa*, ie, the set of complications and clinical phenomena which arise in the patient after a few years of therapy. Very common phenomena such as *wearing-off* or end's dose effect belong to this syndrome. So as the time goes by, the duration of therapeutic effect of the dose was reduced; fluctuations on / off: that is, alternating with short periods of preserved motility, with the presence of involuntary movements (ON STAGE), with periods of marked akinesia, tremor poorly responsive to levodopa (OFF STAGE), with no real correlation with the administration of the drug. The immediate side effects of levodopa are of central or peripheral type. The central effects are related to the dopaminergic exercised effect directly in the CNS, they are represented by the dopaminergic psychosis and marked by symptoms such as hallucinations, delusions, illusions and mental confusion, in the complete absence of negative symptoms (affective flattening). Peripheral effects have gastrointestinal nature.

3.7.2. COMT inhibitor

Entacapone and tolcapone are drugs which reduce the use of levodopa, thus triggering increased availability in the blood. An increased duration of action of levodopa is

achieved, it reduced the wearing-off, it increased duration of ON phase, and the possibility of reducing the dosage of levodopa.

As central side effects, a possible increase in involuntary movements and, rarely, a worsening of the central side effects of levodopa were observed.

3.7.3. Dopamine agonists

The dopamine agonists were initially developed for the treatment of advanced PD , in addition to levodopa, to reduce the dosage and gain control of dyskinesias, without a deterioration of the off phase. Currently they are used in the early stage of the disease too, as monotherapy or in combination with low doses of levodopa, as a strategy to prevent the onset of motor complications and as it was shown that the frequency and severity of fluctuations and dyskinesias in patients treated with dopamine agonists are lower than monotherapy with levodopa.

All dopamiono-agonists, however, determine possible side effects, both central and peripheral level, to be taken into account when you decide to use them.

At peripheral level, the most frequent are: nausea, vomiting, orthostatic hypotension, leg edema.

The central side effects to be considered are psychosis (hallucinations, delusions, confusion, compulsion / addiction), daytime sleepiness and sudden sleep onset and REM sleep disturbances.

In recent decades we described cases of PD patients who developed a disorder of impulse control (ICD) in relation to the assumption of dopamine agonists. Pathological gambling, compulsive shopping, compulsive sexual behaviors or pathological hypersexuality, compulsive computer use were observed in patients with PD who developed the ICD, in addition to compulsive eating and a dependence on dopaminergic therapy. It is important to emphasize that for the development of these disorders play a fundamental role the premorbid patient clinical features (Voon et al. 2010).

In the market there are *ergot* derivatives including *bromocriptine* which was used widely for a non-interference of diet on its absorption (Lieberman & Goldstein, 1992). The limitation of these drugs is the appearance of more side effects than the LD, such as nausea, vomiting, cardiac arrhythmias, hallucinations and compulsions. Weiner and coworkers (1993), Montastruc (1994), Przuntek (1996) and Ruscol (2000) observed that

if the antiparkinsonian therapy is started with these agonists, it reduces the incidence of motor fluctuations along the clinical course.

Pramipexole and *Ropinirole* are two efficient *non-ergot* drugs, both in the initial phase of PD that in the advanced stage (Korczyn et al., 1998). The first one was initially developed as an antidepressant and later it was discovered its effectiveness in the treatment of Parkinson's Disease.

Rotigotine is another agonist drug of levodopa which is administered transdermally. The advantage of this mode of administration is the reduction of daily tablets which the patient must take. Side effects are similar to those of other agonisti drugs and tolerability is good (Parkinson Study Group, 2003).

Finally, there is also the *Apomorphine*, a dopamine agonist very powerful which is administered subcutaneously and reduces parkinsonian symptoms very quickly by mimicking the levodopa's effect (Schwab, 1951; Otzias et al., 1970; Corsini et al., 1979; Colosimo et al., 1994). It is used in the advanced stages of PD, when the motor fluctuations become uncontrollable with standard therapy. Micropumps are used for their infusion, which goes to inject the drug in a continuous way (Obese et al., 1987; Poewe et al., 1988; Ray et al., 1988; Fraknel et al. 1990).

3.7.4. MAO-B inhibitor

• *Selegiline*:it is an irreversible MAO-B inhibitor, which, used in combination with levodopa, may increase the duration of the on period and reduce the dose of levodopa required up to a 25%.

• *Rasagiline*: it is a drug of recent commercialization and it is a potent and irreversible inhibitor of MAO-B, which determines an increase in extracellular levels of dopamine in the striatum.

3.7.5. Amantadine

Initially used as a flu drug, it has shown over the years and with clinical experience to be effective in improving the motor characteristics of a small group of patients with early stage disease. More recently, it has been confirmed its short- and long-term effectiveness in controlling dyskinesias which appears in the advanced stage. Increases dopamine quantities released.

3.7.6. Anticholinergics

Although today is the least used, anticholinergics are the first drugs used for the PD treatment. Their effectiveness is expressed predominantly on tremor and rigidity, they may be useful in patients with drooling too. The central side effects include cognitive deterioration and worsening of psychosis.

3.7.7. Surgical therapy

Treatment for Parkinson's Disease is primarily a pharmacological one and it aims to minimize motor and non-motor symptoms. In some cases, during the normal course of the disease, drug therapy is not able to control the symptoms and the patient can have unpleasant side effects (Stocchi, 2008). Surgical therapy is valid therapeutic option to treat symptoms in advanced stages of the disease. Thus the *Deep Brain Stimulation i*s born (DBS) (Figure 6), which is based on the fact that the degeneration of the substantia nigra pars compacta causes an overactivation of the sub-thalamic nucleus (NRC) and the inner core of the globus pallidus (Gpi). With DBS you go to inactivate these two structures and to improve PD symptoms (Peppe, 2009).

A further advantage of this type of therapy is the reduction of the assumption of total daily levodopa (Athanasia, 2005). A research of Athanasia and collaborators (2005) has shown that the the pharmacological treatment can be significantly reduced following the DBS surgical treatment. The PD medications can be reduced by about 40-50%, and this reduction lasts for about five years. By contrast, it has been observed an increase of antidepressant drugs, subsequent to stimulation. DBS involves introduction of a four-pole stimulator electrode which is connected to a subcutaneous pacemaker through an extension cord. This causes a high-frequency stimulation which blocks the functionality of the anatomical-target structure, in this case the NRC and the Gpi. The advantages of this procedure are the reversibility and the possibility to vary the parameters with the ability to self-manage the stimulator. The result of these steps is for 80-85% positive. The main risks are generic ones like a surgery to which we must add the risk of intracranial bleeding and a possible tract infection implanted. These episodes occur in about 1-2% of cases (Carrara, 2014). Not all patients, however, are candidates for this type of treatment. The indication for this type of stimulation's intervention is rare; the

decisive factors to determine the suitability of the intervention are the disease trend, the symptom, age and living situation of patient.

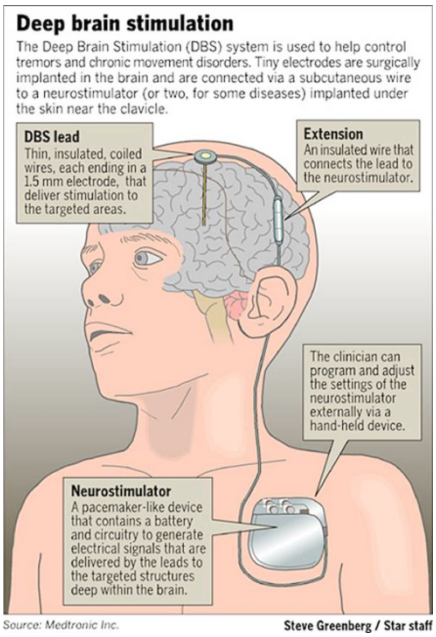


Figure 6: *Deep Brain Stimulation (Medtronic Inc)*

3.7.8. Non-motor symptoms' treatment

In many patients the presence of secondary symptoms can be even more annoying the sole presence of motor symptoms. These symptoms should be adequately treated to improve the quality of life of people with PD.

An outcome reported by many patients is insomnia. If it is caused by a difficulty in performing the movements in the bed during the night, the therapeutic strategy will be to balance the best daily dose of levodopa. Often to counter feelings of fatigue and avoid falling asleep during the day may be prescribed cures (Pezzoli, 2009). It is important to keep controlled even the RBD by medication.

For the treatment of anxiety and depression, they usually prescribed SSRIs (*selective serotonin reuptake inhibitors*), which together with an adequate psychological support may help the patient to participate better in social life.

Mental disorders are often present in Parkinson's Disease and it must be stressed that all of the anti-parkinsonian drugs are able to induce psychotic symptoms such as hallucinations, delusions and confusion. In the event of a psychotic disorder doctor may prescribe specific antipsychotic drugs.

For orthostatic hypotension it is not normally prescribed medications but you suggest any precautionary measures such as lying down with legs raised increasingly, a diet rich in sodium and administration of small meals and divided over the day (Pezzoli, 2009).

4. ATYPICAL PARKINSONISM

There are many clinical forms that resemble Parkinson's disease but in reality are not. From about 10-15 years, we talked about primitive parkinsonism, when there is an unknown cause, and secondary parkinsonism, when the cause is instead known (Table 2). Usually the diagnostic dilemma arises when symptoms onset aren't unilateral and when the patient does not respond to levodopa therapy. Another alarm bell is when the patient has immediately hallucinations and confusion.

PRIMITIVE PARKINSONISM	SECONDARY PARKINSONISM
Idiopathic Parkinson's Disease	Parkinsonism Vascular Disease
Multisystem Atrophy	Parkinsonism by drugs
Lewi Body Disease	Neurotoxins' Parkinsonism
Progressive Sopranuclear Palsy	Parkinsonism Post-traumatic
Corticobasal Degeneration	Parkinsonism Associated with other primitive nurological disease
	Dysmetabolic Parkinsonism

***Table 2**: Classification of main parkinsonism.*

Atypical parkinsonism are a group of specific neurodegenerative diseases characterized by the association of parkinsonian signs with other neurological signs. They are characterized by an evolution faster than the more common clinical Parkinson's disease which determines, therefore, a more debilitating functional prognosis.

There are no biological markers which enable a reliable diagnosis of atypical parkinsonism, which is then still mainly based on the presence and progression of various symptoms; diagnostic confirmation will only post-mortem examination.

The three main forms of atypical parkinsonism are represented *multiple system atrophy*, *progressive supranuclear paralysis* and *corticobasal degeneration*.

4.1. Multiple System Atrophy

The multiple system atrophy term was introduced for the first time in 1969 by Graham and Oppenheimer to indicate a neurodegenerative disease characterized clinically by a

variable combination of signs and autonomic symptoms, parkinsonian, pyramidal and a cell loss in the basal nuclei and in olive system -ponto-cerebellar (Stefanova et al. 2009). Since then, it has been possible to group under a single nosological entity diseases such as the olive-ponto-cerebellar atrophy, idiopathic orthostatic hypotension, Shy-Drager syndrome and nigrostriatal degeneration.

Based on the most recent discoveries in the field of molecular pathology MSA was finally recognized as an α-sinucleopatia[2] along with Parkinson's disease and dementia with Lewy bodies.

4.1.1. Pathogenesis

The most affected structures are the basal ganglia, the hypothalamus, the locus coeruleus, the pons and the cerebellum, the bulb and the spinal cord (Stefanova et al. 2009).

The multiple system atrophy (MSA) is a parkinsonian framework that is characterized by rigidity, bradykinesia, and postural instability. The MSA differs from MP due to degenerative changes of the brain, the corpus striatum, thalamus and subcortical structures such as the hypothalamus, in addition to the lesion of the substantia nigra.

The clinical picture is determined by the variable combination of dysfunction signs about extrapyramidal, cerebellar, pyramidal and autonomic systems. Currently, the MSA is categorized into two basic forms: MSA-P, where the predominant parkinsonian symptoms, and MSA-C, which are more evident signs of dysfunction of the cerebellar system (Wenning et al . 2004). The prevalence of MSA varies from 1.0 to 4.9 per 100,000 and is more common in individuals with more than 50 years, with an average onset in the sixth decade of life. The average survival is between 7 and 9 years for both subtypes. The sudden death and pneumonia are the two most frequent causes of death in these patients (Tada et al., 2007). In addition, the older onset and early dysautonomia are factors predictive for rapid disease progression and reduced survival (O'Sullivan et al., 2008). In Western countries the MSA-P covers 80% of patients. It characterized by akinesia and stiffness poorly responsive to levodopa, postural tremor in the hand,

[2] The α-synuclein is a pre-synaptic protein belonging to the synucleins family, implicated in neuronal plasticity and neurotransmission processes through interaction with the synaptic vesicles. Although it has been highlighted the involvement of this substance in the pathogenesis of some forms of MP, it is still no mutation was found on the gene in MSA.

impaired postural stability and cranio-cervical dystonia. The other subtype, MSA-C, is dominated by a progressive ataxia posture, gait and limbs, dysarthria, and impairment of cerebellar ocular motility.

Currently, the diagnosis of MSA and PD are based primarily on the clinical history and physical examination; however, neuroimaging technical specifications function and structure can help the clinician in the differential diagnosis.

In particular, neuroimaging findings are now included in the new diagnostic criteria as additional features which support the diagnosis of possible MSA (Gilman et al., 2008), between these putaminale the pontine atrophy or MRI and hypermetabolism putaminale or cerebellar PET with fluorodeoxyglucose (FDG-PET).

4.1.2. Clinical features

The average age of onset is between fifty and sixty years with a higher incidence in males, and a median survival of 7-9 years for both forms (Parikh at al. 2002). One difference, however, has been highlighted in more rapid deterioration of motor functions in MSA-P.

Motor symptoms consist mainly of parkinsonian aspects present in 89% of patients diagnosed with MSA and are the classic signs of PD (akinesia, rigidity, tremor and postural deficits). In the early stages of the disease, Parkinsonian symptoms do not exhibit the characteristics which enable sure to distinguish between the two diseases. However, the progression of motor symptoms in the course of MSA is usually much more rapid and the loss of autonomy takes place in a short time. The MSA patients, treated with levodopa, often do not develop the typical dyskinesias of the MP, but the dystonia of the facial muscles. Dystonias, on the other hand, are part of the phenomenology of the disease, as it is demonstrated by the appearance of the Pisa syndrome (characterized by severe tonic flexion of the trunk, the head and neck).

Other unusual aspects that should guide the diagnosis are: early onset of falls, urinary disorders, early onset of dysarthria, trembling and scanned, and associated early in hypophonia and dysphagia, stridor day and night with sleep apnea and emotional incontinence (Antonini & Barone, 2008). For these reasons, the atypical symptoms are not identified early, and in most cases a therapy with L-dopa is initiated, with a good response in the early stages of the disease in a small percentage of patients and a rather poor response in most patients. The cerebellar signs are present in about half of patients

and usually involving the torso and limbs, resulting in an obvious difficulty of the march.

The signs to burden down the Vegetative Nervous System (VNS) are very common and affect up to 97% of patients with MSA (Wenning et al. 1994). The most frequent are those affecting the cardivascular system and genitor-urinary.

Cognitive function in the MSA do not seem to be involved. Neuropsychological tests show a slight impairment of the frontal functions, not dissimilar from those found in P, however, with a possible greater attention deficit. The MSA patients do not present alterations of language, visual perception, spatial recognition or praxis.

In the MSA neuropsychiatric disorders are often similar to those observed in PD, infact, it is basically characterized by affective disorders and sleep disorders.

However, compared to the body of work conducted in patients with PD, these aspects have been investigated in the MSA only in a few works.

The affective disorder most frequently reported in patients with MSA is depression, that can be a first symptom of the disease (Goto et al., 2000) and which, while not being correlated to motor disability, is present in over 80% of MSA patients with a majority autonomic expression (Gill et al., 1999).

Actually, considering the MSA patients with prevalence of parkinsonism, the percentage of depressed patients is less, being about 40%, however, representing a condition able to determine by itself a significant decrease in quality of life of these patients (Benrud-Larson et al., 2005).

By comparing the percentage of depressed patients with MSA and PD patients, there are not significant differences between the two groups, despite the greater highlighted disability by MSA patient (Benrud-Larson et al., 2005). In an attempt to differentiate mood characteristics of MSA and PD patients, a study showed that MSA patients manifested most commonly disorders characterized by feelings of indifference while subjects with PD showed more anxiety; administration Levodopa produced a marked improvement in depressive symptoms in PD patients, while the emotional indifference of MSA patient did not change substantially following the dopaminergic stimulation (Fetoni et al., 1999).

Behavioral disorders during REM sleep are frequent in the MSA. These episodes are characterized by loss of normal muscle weakness with onset complex motor activity associated with dreaming.
These manifestations may precede the onset of many years of neurological symptoms.

4.1.3. Therapy

Currently there is no effective therapy that can change rapidly and devastating progression of MSA and there are only a few randomized controlled clinical trial. The treatment of the MSA is disappointing, since, unlike the PD levodopa is partially effective and only in the earliest stages of the disease. The majority of patients show a very poor response to levodopa, although a good response was reported in 20% of the patients, which is maintained over time only in 13% of cases (Wenning et al. 1994).
Unlike the PD psychotic disorders induced by levodopa, appear to be less common in MSA (Wenning et al. 1994). In addition, in half of the patients, it was observed the onset of dyskinesias predominantly affecting the oro-facial and prematurely assume the dystonic character.
It has not been reported an effective response to dopamine agonists, as they proved ineffective both amantadine that anticholinergics, which can reduce stiffness and tremor, but exacerbate other symptoms, such as gastrointestinal and urological disorders.
Initial approaches to the treatment of MSA with the functional neurosurgery have been disappointing.
Even the treatment of other symptoms, especially those affecting the autonomic nervous system, often does not guarantee satisfactory results.
Because of the limited effectiveness of drug therapies, patients suffering from this serious disease must enter into a structured treatment program, where physical therapy, speech therapy and occupational therapy to reach a priority placement. It will therefore be important to advise the patient and family the possible complications of the disease course.

4.2. Progressive Sopranuclear Palsy

"The patient has hard and very rare winking eyes, a retracted head, a reduced to an indistinct rumble voice,a awkwardly and so unsteadily walking with great tendency to

fall backward. The motor imprudence is an early feature and in many cases it leads to a rocket typical sign in rising from a chair. Clothes are soiled with food, because the patient is not able to look down toward the plate and he has difficulty swallowing. The patient takes time to answer longer than normal because of the slowing of cognitive processes ." (Ravizza, 2004)

The first clinical description of Progressive Supranuclear Palsy (PSP) dates back to 1909, when Janischewsky described a patient who probably had the disease. It is really possible, that clinical cases of PSP were also described previously, for example a 1889 photograph shows a patient suffering from a Charcot parkinsonian syndrome (Goetz et al. 1996).

To these first descriptions other clinical and pathological reports were followed until 1964 when Steel, Richardson and Olzewski systematically described the disease as a condition which affects the brain stem and the basal ganglia causing a clinical picture of paralysis of vertical gaze palsy pseudo bulbar, dystonia, and dementia (Brusa et al. 1980).

4.2.1. Pathogenesis

The PSP was described for the first time in 1964 by Steel, Richardson and Olszewski as a disturbe involving the brain stem, the basal ganglia and the cerebellum causing paralysis of vertical gaze, pseudobulbar palsy, nuchal dystonia and dementia fronto-limbic (Steel et al., 1964). It is only in the last decade, however, that the PSP was best characterized in terms of neurobiology, epidemiology and clinical (Hauw et al., 1994; Bennett et al., 1995; Schrag et. Al, 1999; Colosimo et al., 2003). In particular, several studies have shown that this is not a rare disease, having an adjusted prevalence by age 5-6 / 100 000, with a mean age at onset of 65 years and a mean disease duration of 5-7 years (Schrag et al. 1999). It has not yet been possible to identify certain risk factors for the disease. Probable pathogenetic mechanisms may be pathological activation of glia, lack of neurotrophic factors and abnormalities in the *tau* gene.

The PSP is therefore part of the tauopathies family, in which the tau protein abnormalities, associated with microtubules, causing neuronal degeneration in different brain regions.

The PSP, considered a sporadic disorder, is characterized by neuronal loss, gliosis, and accumulation of tau protein in the brain areas involved. The presence of these proteins in neurons is revealed under forms of neurofibrillary plaques. The tau protein has the physiological role of establishing and maintaining normal neuronal morphology and therefore to ensure neuronal function.

The movement disorders associated with this disease depends largely on the striatal dopaminergic deficits leading to increased thalamic inhibition on the motor cortex.

The involvement of frontal and dorsolateral prefrontal cortex and caudate nucleus are at the origin of bradykinesia, and behavioral disorders such as apathy, premature and very frequent, or more rarely disinhibition, dysphoria and anxiety, as well as deficits in executive functioning, dependent lesions in the frontal cortex.

4.2.2. Clinical features

The age of PSP onset is typically between 60 and 65 years, with no significant difference between the sexes. The median time from illness onset to death varies between 5 and 9 years old, while the average interval from symptom onset to diagnosis varied between 3 and 5 years, which means that for the majority of patients the diagnosis is wrong for much of the disease progress, mainly misdiagnosed concern PD, balance disorders, stroke and depression (Antonini & Barone, 2008). Moreover, it is not uncommon that the patient is sent to the eye for the early onset of visual disturbances. The postural instability with frequent falls, typically backward, and paralysis of vertical gaze are typical symptoms of this neurodegenerative disease.

Behavioural disorders are, although not always very early, important, especially apathy and disinhibition occur more frequently than in the PD (Aarsland et al. 2001). Even an early neuropsychological evaluation can help in the process of differential diagnosis of parkinsonian syndromes, revealing the PSP disturbances of executive functions.

The patient with PSP was found to have personality changes and, more rarely,aggression.

In the original work of Steele, Richardson and Olszewski 1964, six patients out of nine described, presented personality changes such as irritability, suspiciousness and carelessness. In one case it was described the presence of reactive depression and two subjects exhibited emotional lability.

In one of the first Italian papers published on the PSP, it was shown that disorders personality could constitute one of the essential traits of the disease from the outset (Brusa et al., 1980). This observation was later confirmed by other studies: the presence of *mental disorders*, arose prior to the onset of typical motor disorders of the PSP and present then at an early stage of the disease, it is reported in 46% of patients (Kristensen, 1985).

The early onset of behavioral symptoms, such as personality changes, depression, apathy and euphoria, often involves the formulation of erroneous diagnosis of dementia or psychosis in patients who subsequently develop typical signs of PSP (Lees, 1987).

Behavioural disorders, most frequently reported in patients with PSP, include apathy (91% of cases), disinhibition (36%), dysphoria and anxiety (18%), irritability and agitation (9%) (Litvan et al., 1996).

However, these disturbances do not completely describe the spectrum of neuropsychiatric changes which is observed in patients with PSP.

In that regard, it was suggested that neuropsychiatric disorders in the course of PSP could are grouped into three main categories (Chiu, 1995): cognitive disorders, affective changes and behavioral psychotic symptoms.

As for the cognitive disorders, a ideational slowdown is reported in 69% of patients with PSP (Chiu, 1995); this condition, also described as bradypsychia, together with other cognitive disorders such as the presence of imitation / utilization behaviors and perseverative, set up a framework of *subcortical dementia* due to dysfunction the frontal lobes and clearly distinguishable from a framework of *cortical dementia* typical of Alzheimer's disease (Albert et al., 1974). Affective and behavioral changes include several events ranging from emotional lability with laughts and / or crying spastic impairment of expression pseudobulbar, to potentially dangerous behaviors.

The slowing of thought processes may mask an underlying condition depression, characterized by blunted affect, absence of suicidal ideation and poor response to antidepressant drugs, with the exception of the few cases where amitriptyline would produce significant improvements (Kvale, 1982).

With regard to the psychotic symptoms, rarely they have been reported cases of PSP with ideation and paranoid hallucinations (Chiu, 1995). In this regard, comparing the psychiatric symptomatology of patients with PSP and PD patients, it was shown that in

the MP the presence of hallucinations and depression is more frequent, while in the PSP it is observed more commonly apathy and disinhibition, suggesting greater dysfunction of the streets orbital-frontal and frontomediali non-dopaminergic the PSP than the PD (Aarsland et al., 2001).

4.2.3. Therapy

Pharmacological treatment of PSP remains inadequate and insufficient.
An audit carried out on 12 cases with pathological diagnosis of PSP concluded that the use of levodopa, dopamine agonists, anticholinergics and amantadine is largely ineffective and frequently associated with side effects (Antonini & Barone, 2008).
Currently in Italy an experimental study to evaluate the effect of treatment with stem cells is ongoing (Giordano et al., 2014; Canesi et al., 2016). The one year after cell infusion results, in all treated patients, show the motor function rating scales remained stable for at least six-months during the one-year follow-up (Canesi et al., 2016).

4.3. Corticobasal Degeneration

Corticobasal degeneration (CBD) is a rare neurodegenerative disease described for the first time at the end of the 60s, which is manifested by a disorder of the akinetic-rigid movement, not responsive to levodopa associated with cortical and behavioral dysfunction (Rinne et al., 1994; Girotti & Fetoni, 2010).

4.3.1. Pathogenesis

The etiology of CBD remains unknown, but it seems to be correlated with mutations in the gene linked to tau protein. The differential diagnosis is often difficult, particularly in the early stages, because the clinical symptoms are similar to those found in other neurodegenerative diseases such as PD, MSA, PSP.
As in other neurodegenerative diseases, there is no specific therapy.
The CBD is characterized by asymmetric atrophy of the frontal and parietal lobes and by depigmentation of the substantia nigra. The core sub thalamic, the side of the thalamus, the globus pallidus and the red nucleus are affected by the degeneration too.
The diagnostic level while MRI is rarely demonstrative, PET highlights often hypometabolism of the frontal areas medial and basal ganglia (Rea et al., 2007).

The neuropathological examination remains critical to the diagnostic definition of CBD, which shows a severe posterior parietal and frontal cortical atrophy. The cortical areas motor way are markedly impaired. The cortical atrophy tends to be asymmetrical and it is prevalent in the most affected hemisphere contralateral limb (Girotti & Fetoni, 2010).

4.3.2. Clinical features

The onset is almost always unilateral, represented by rigidity, dystonia and apraxia of a limb. Over time, the disturbances may extend to the other side of the body and may appear other symptoms as dysarthria, gait deficits, tremor action and cognitive deterioration (Antonini & Baron, 2008).

The CBD manifests between 60 and 80 years, with equal incidence between the sexes (Rea et al., 2007). The disease has gradually evolved with an average duration of 7-10 years.

The main onset symptom proved is the involvement of an upper limb such as to render it useless (apraxic limb, rigid and dystonic), followed by gait disturbance; manifestations of onset less frequent, however, they may be sensory disturbances, speech disorders and behavioral abnormalities (Rinne et al. 1994).

As already mentioned, apraxia is often asymmetric and most of the times ideomotor: it presents as an inability to imitate no meaning or symbolic gestures.

Another sign of common observation in the CBD is the alien limb phenomenon, defined as the subjective feeling that one limb is foreign, it does not belong to his body, associated with the presence of involuntary motor activity of the same. Frequently, the patient grab with a limb a portion of their body, clothes, objects or persons present in its range. Many patients are unaware of the movements made with the alien limb and they show some signs of neglect. A conflict is typical, because the affected limb interferes with the healthy limb voluntary activities.

The presence of signs of cognitive impairment are considered as elements to support the diagnosis. In fact, a specific pattern of cognitive impairment accompanies and may precede the motor disorder to pose a fundamental aspect of the disease (Graham et al. 2003).

Cognitive impairment of the CBD is represented by executive function, gestural, visuospatial, calculation and language disorders, which are associated with a relative preservation of semantic memory. The memory deficit disorders consist of episodic

memory less severe than in AD patients, especially because they are linked to search problems rather than storage. This pattern of cognitive deficits is closely related to the neuropathological damage, located in frontal and parietal cortex, which in addition to the basal ganglia.

The relatively high prevalence of dysfunction language differentiates the CBD by the PD and other parkinsonisms. CBD patients also show a dysexecutive syndrome with planning deficit, abstraction and control. As regards the psychic disorders these may be present performance varied: depression, apathy, irritability, agitation are common; less common instead delusions, disinhibition and compulsive symptoms (Cummings & Litvan, 2000). Other psychic manifestations, less frequent, however, are anxiety, obsessive-compulsive symptoms, emotional lability, impaired judgment, impulsivity, perseveration, changes in social behavior (*ibid*).

4.3.3. Treatment

There is no specific therapy, or drugs with a satisfactory symptomatic effect or which slows the progression of the disease (Kompoliti et al., 1998). Levodopa has a limited efficacy and its use may be accompanied by dyskinesias. The dopamine-agonist drugs have a lower effect and still more frequently give rise to side effects.

5. THE RESEARCH

Artistic creativity can be studied by neurological perspective, particularly in neuroanatomic and neurobiological field.

It is known that neurological conditions can alter and influence the artistic production: Maurice Ravel, Vincent Van Gogh, Francisco Goya, Giorgio De Chirico, Salvador Dali and recently the great contemporary painter Willem de Koonig are some famous cases which can be remembered (Mendez, 2004).

In Frontotemporal Dementia (FTD) an increase of creativity in music, math and visual - but not in the literary or poetic field was observed. New artistic skills can also arise during the genesis of the disease in FTD patients who before that time do not show particular creativity in painting (Mell et all., 2003; Miller et all., 1996). During the development of FTD they were found changes of the pictorial style which would tend to become less formally structured, more expressive, more vivid, saturated colors and pictorial stroke mode far from realism, impressionistic and less detail.

Relative to Alzheimer's Disease (AD), if sometimes was observed loss of expressive content, change the color and spatial sense of organization and figural trend towards simplification iconographic, pictorial talent loss, other times it has been observed - during the progressive cognitive impairment detectable in various spheres - that pictorial creativity can persist even up to the last stages of the evolution of the disease. In such cases the pictorial stroke shows *surrealistic* characteristics and less focus on the details. But the artistic quality would be preserved (Piechwski-Jozwiak & Bogousslavsky, 2013; Miller, et al., 2004; Crutch et al., 2001; Espinel, 1996). Various neurological hypotheses were proposed to understand the evolution of different creative ways in FTD and Alzheimer's patients, both in neuroanatomical and functional circuits (*Ibid.*). The connection between parietal and temporal lobe in the creative process is emphasized by studies with AD patients who developed an increase of artistic production. Furthermore, hippocampal and temporoparietal areas atrophy would not think of an appearance of new capacity (Miller & Hou, 2004; Crutch et al., 2001). There are exceptions such as a case study of a painter who developed dementia and continued to paint despite the progression of the disease (Fornazzari, 2005).

The case of the contemporary painter Willem de Koonig is known and studied (Espinel 1996), he suffered from AD and his artistic production passes, in the course of four

decades, from realism to abstract art. The last artistic period of Willem de Kooning is located in search of a new way of painting; in the period between 1983 and 1986, the most prolific one, he produced nearly a painting a week and at the end of 1987, his health began to deteriorate gradually; in 1990, at age 86, he abandoned painting. The art of de Kooning of those years lost many of the characters of the previous one and it seems closer to a classicism which, for its lyrical, architectural and idyllic character, with the dominant use of primary colors, gave reminiscent of Mondrian (Espinel, 1996). Painting is airy in the application of color, with large white spaces which accentuate the brightness, thus appears to us an unknown and flowing calm, devoid of the legendary artist's dissatisfaction (*Ibid.*).

Almost absent is the literature on the creativity of artists diagnosed LBD (Lewy Body Disease). In this sense very intersting is the study of Drago, Crucian, Foster, Cheong (2006) in which the production of a painter diagnosed LBD was evaluate before and after the onset of the disease. The study highlighted the decline of painting skills after the LBD onset except for the *novelty* parameter. It was assumed that such a loss of creative dimension may be related to a deterioration of parietal lobes which would damage the representation iconic.

In PD patients it was observed that the disease onset does not necessarily damage the artistic expression already present. Even after the diagnosis of PD and subsequent onset dopaminergic treatment can increase creativity in exuberant and even compulsive manner. These phenomena were observed both in the figurative and literary creativity.

Biochemical dopamine's level seems to play an important role in artistic manifestations of PD patients (Schwingenschuh et al., 2010; Inzelberg, 2013). Several studies found that after the introduction of dopaminergic therapy, some patients showed a marked creativity. These new creative talents would not only be the side effect of an impulse control deficits, collateral symptom to dopamine agonist therapy, despite these patients remain engaged in their creations for several hours the day (Canesi et al., 2012). Canesi and co-workers stated that probably these patients, became creative, were already predisposed to think in different ways (*to diverge)* and began to paint, or make sculptures, following the administration of dopaminergic therapy. The dopaminergic therapy, by increasing the level of dopamine, would be to unmask an ability remained

undetected for many years. The authors emphasized the fact that the correlation between the dopaminergic therapy and the appearance of artistic thrust is not so direct.
Other authors, however, as Bindler and coworkers (2011) argued, in conclusion of their study, the obvius correlation between dopaminergic drugs and the emergence of artistic talent. These authors think that the link between therapy and creativity is twofold. On one side, drug therapy would allow the patient to take a creative activity understood as an attempt at sublimation, i.e. the creative hobby allows the patient, already forced to leave social and work activities, to get better. On the other side, the increased creativity is the direct consequence of therapy: a behavioral disinhibition. The authors conclude their article with this sentence summary of their thought: "Did the dopamine agonist drugs become the creativity drug?" (Bindler et al., 2011).
However, the obsessive character of artistic creativity of PD patients on dopaminergic treatment is put in relation with the dopamine agonist therapy in combination with L-DOPA / carbidopa, in conjunction with functional deficits of frontal or temporal lobes. The unusual and significant increase of creativity was put also in relation hypomania resulting in over-stimulation of dopamine receptors.
The creative subjects have probably brain structures which are capable of storing extended and specialized knowledge in the temporal-parietal cortex, they are endowed with the ability to process the "divergent thinking" mediated through the frontal zone and to modulate the transmission of norepinephrine in such a way that during the creative process of this neurotransmitter levels decrease (Heilman et al., 2003).
Purpose of this research is precisely to broaden the knowledge on creative processes and their neurofunctional substrate, through a study of a cohort of diagnosed patients with idiopathic PD and atypical parkinsonism (MSA, PSP, CBD). Assuming that in these diseases are involved different neural circuits, and, consequently have a different phenotype of symptoms, we want to check the progress of divergent thinking (measurable declination of creativity).

5.1. Subject selection

We conducted a prospective case-control study at the outpatient clinic of the Parkinson Institute (ASST Gaetano Pini-CTO, Milan, Italy). First, consecutive PSP patients were screened for inclusion. Then, we recruited two additional group of patients: MSA

(matched [1:1] by gender, disease duration [±1 year], age at onset [±1 year] and education [±1 year]) and PD (matched [1:1] by gender, education [±1 year], age at assessment [±1 year] and disease severity [Hoehn-Yahr stage; (Hoehn & Yahr 1967)]. PD patients could not be matched by disease duration due to the more benign course of the disease. Finally, a group of HC (matched [1:1] by gender, education [±1 year] and age at assessment [±1 year]) was studied. An exploratory evaluation of a small group of CBD patients was also conducted. Due to the limited number of assessable patient suffering from this disease no matching procedure was taken into account.

Probable MSA and PSP were diagnosed in according with the criteria provided in the second consensus statement on the diagnosis of Multiple System Atrophy and the National Institute of Neurological Disorders and Stroke/Society for Progressive Supranuclear Palsy diagnostic (NINDS/SPSP) (Gilman, 2008; Litvan et al., 1996). Idiopatic PD was diagnosed in agreement with the UK PD Society Brain Bank criteria (Rowe et al., 2008) .

All patients and HC had to be cognitively preserved (Mini Mental State Examination [MMSE] score>24/30 points) (Folstein et al., 1975 and nobody played creative work as professional jobs or hobby. Patients treated with neurosurgical procedures were excluded and none of HC included was caregiver or family member of study patients (community controls). None of the subjects have a psychiatric history.

All subjects gave written informed consent before being submitted to the experimental evaluation.

5.2. Assessment protocol

A standardized neuropsychological battery was also administered to evaluate cognitive, visuo spatial and frontal functions. To assess these cognitive functions we used:

- Mini Mental State Examination (MMSE) to a global cognitive assessment tool, consisting mainly of verbal tasks (Folstein et al., 1975);
- Clock Drawing Test (CDT): tool which allows an overall assessment, the patient is asked to write the clock numbers within a circle at the end, it is required to draw lancets that mark 11.10 (Shulman, 1993);
- Frontal Assessment Battery (FAB): this battery allows a global assessment of executive functions, consists of six separate tests which assess the

capacity for abstraction, abstract thinking, cognitive flexibility, motor planning and control impulsivity (Dubois et al., 2000).

The battery of neuropsychological texts was built on the basis of the clinical features of patients with PSP and MSA.

The Abbreviated Torrance Tests of Creative Thinking for Adults (ATTA) (Torrance 1974), was used to assess creativity. ATTA consists of three activities, one verbal and two visual-spatial.

The question of the first activity which is proposed by the examiner is as follows:

> " *Now I will present an unlikely situation and a situation that will never happen. Try to suppose that it really happened. You have the ability to use all your imagination to think of all the interesting and exciting things that would happen if this situation were to really happen. In your imagination, try to assume all the things which would happen after that. Make the largest possible number of hypotheses and assumptions. The situation likely is the following: try to assume which attacked to the clouds there are the strings that dangle down toward the ground. What would it happen? Make a list of your ideas and assumptions ".*

The second visual-spatial activities, however, is to give the subject a sheet with two incomplete drawn images and to ask him to create, starting from the stimulus provided, a design with a meaning and to give a title to the paint created.

The third activity, instead, consists of providing to the subject a printed sheet with nine pairs of parallel lines, from which, will have to draw the largest number of possible paints.

The subject is specified that each design must be meaningful and for each image will have to invent a title. For the completion of each task the subject will have 5 minutes of time.

The evaluation of each test will be independent of the score obtained in the neuropsychological tests. The scoresof each round will be awarded according to four dimensions of creativity: fluency, flexibility, originality and elaboration. Briefly, the fluency was defined as the total number of different responses in the first activity and the total number of designs produced by the incomplete figures in the second activity and the parallel lines of the third. Originality is defined primarily by the degree of novelty-rarity of the responses provided in the first activity, and the ability to create unusual and new designs in the activities 2 and 3. The elaboration, however, is defined

by the ability to embellish drawings with the addition of details. Flexibility, finally, is defined as the ability to create different responses from the same stimulus.
On the same day, clinical work-up included the evaluation of disease severity and motor functions by means of the Hoehn and Yahr (H&Y , in worst "OFF" conditions) staging system (Hoehn & Yahr, 1967) and the Unified Parkinson Disease Rataing Scale (UPDRS) part III (motor score, in best "ON" conditions; Fahn & Elton, 1987), respectively. Although specific scales for PSP (PSP rating scale) and MSA (UMSARS) (Wenning et al., 2004) are available, we used UPDRS part III to measure and to compare disability conditions in the different neurodegenerative diseases. Information on dopaminergic treatment was also recorded in all study groups and doses of dopaminergic medication were converted to equivalent levodopa doses (LEDDs) (Tomlinson et al., 2010).

5.3. Statistical analysis

Sample size was calculated on the difference in primary outcome variable (ATTA total score) between PSP patients and healthy controls. Considering a meaningful difference in total ATTA scores of at least 20 points and a common standard deviation of 18 points (Canesi et al., 2015), the sample size sufficient to have a power of 80% with a type I error of 5% is 13 patients in each group.
Continuous variables were reported as mean and standard deviation (SD) and compared between groups using the Student's t-test for paired data with exeception of the comparison with CBD patients (test for unpaired data). Categorical variables were presented as count and percentage.
All data were analyzed using MedCalc Statistical Software version 16.8.4 (MedCalc Software bvba, Ostend, Belgium), setting the level of significance at a two-tailed P-value of <.05.

5.4. Results

The sample of subjects is divided into 4 groups: PSP, MSA, PD patients and HC. Each group consists of 13 subjects (7 males and 6 females). A fifth group was also investigated. It consists of CBD patients, however, as already mentioned. This group consists of only 4 subjects (1 male and 3 females) for the patients' difficulty which

suffering from this disease to undergo the evaluation. Demographic and clinical characteristics are shown in Table 1. Taking into account the less severe progression of PD and the choice of matching by disease severity, as expected, PD patients were characterized by younger age at onset and longer disease duration. However, PD patients still presented less severe motor disfunction than PSP patients. No differences were found in motor disability between PSP and other parkinsonian syndromes. Neuroimaging data confirm the diagnosis for all patients.

***Table 3**: demographical and clinical data of subject.*

	PSP (N=13)	MSA (N=13)	PD (N=13)	HC (N=13)	CBD (N=4)
Male gender, N (%)*	7 (53.8)	7 (53.8)	7 (53.8)	7 (53.8)	1 (25)
Education, M (SD)*	9.7 (3.8)	10.6 (4.8)	10.5 (5.1)	10.5 (3-6)	12.0 (5.3)
Age at assessment, M (SD)*	66.7 (4.3)	65.2 (6.2)	65.0 (11.9)	66.0 (6.2)	71.0 (7.0)
Disease duration, M (SD) §	4.7 (1.7)	4.6 (2.4)	9.6 (6.4)	-	3.5 (1.0)
Age at onset, M (SD)	62.0 (4.9)	60.3 (7.3)	55.0 (10.5)	-	67.5 (6.6)
UPDRS-III, M (SD)	42.2 (8.8)	36.8 (9.5)	32.5 (7.5)	-	36.0 (5.7)
H&Y stage, M (SD) ‡	3.5 (0.7)	3.4 (0.6)	3.1 (0.3)	-	2.8 (03)
LEDDs, mg/die, M (SD)	292 (262)	533 (472)	468 (257)	-	-

Abbreviations: PSP, Progressive Supranuclear Palsy; MSA, Multiple System Strophy; PD, Parkinson's Disease; HC, Healthy Controls; CBD, Cortico-Basal Degeneration; LEDDs, levodopa equivalent daily dose; H&Y stage, Hoehn & Yahr stage; UPDRS- III, Unified Parkinson Disease Rating Scale part III (motor score).
* Common matching variable
§ Additional matching variable for PSP and MSA patients
‡ Additional matching variable for PD patients

Results of neuropsychological tests are presented in Table 2 (Figure 1). In presence of normal cognitive functions, PSP patients were characterized by more impaired frontal functioning (FAB) than HC and both PD and MSA patients, while a trend to significance was observed for the comparison of CDT test with CBD patients and HC. Significantly lower values ($P<0.05$) in FAB were also observed in MSA and CBD patients compared to controls. MSA patients showed also lower CDT score than HC ($P<0.05$). Reading CBD data, we must keep in mind the different size of the sample, so we can speak only about trends. All patients are cognitively intact, in fact the results obtained at MMSE and CDT are in normal range, however, a qualitative analysis of CDT protocols noted an increased presence of errors in patient groups (PSP, MSA, PD). None of the subjects were positive at ICD (Impulse Control Disorder) evaluation.

Table 4: Neuropsychological evaluation

Test	PSP M(SD)	MSA M(SD)	PD M(SD)	HC M(SD)	CBD M(SD)	P-value*	P-value§	P-value‡	P-value†
MMSE	27.0 (1.3)	26.8 (1.4)	26.9 (2.0)	26.7 (1.1)	27.2 (2.3)	0.72	0.90	0.35	0.88
FAB - adjusted score,	12.5 (2.4)	14.8 (1.5)	15.0 (2.2)	16.1 (1.1)	11.7 (3.1)	0.019	0.022	<0.001	0.66
CDT	3.3 (1.3)	2.8 (1.2)	3.7 (1.4)	4.2 (1.1)	4.9 (1.2)	0.25	0.54	0.08	0.07

Abbreviations: PSP, Progressive Supranuclear palsy; MSA, Multiple System Atrophy; PD, Parkinson's Disease; HC, Healthy Controls; CBD, Cortico-Basal Degeneration; MMSE, Mini Mental State Examination; FAB, Frontal Assessment Battery; CDT, Clock Drawing Test.
* PSP vs. MSA by paired t-test
§ PSP vs. PD by paired t-test
‡ PSP vs. HC by paired t-test
† PSP vs. CBD by unpaired t-test

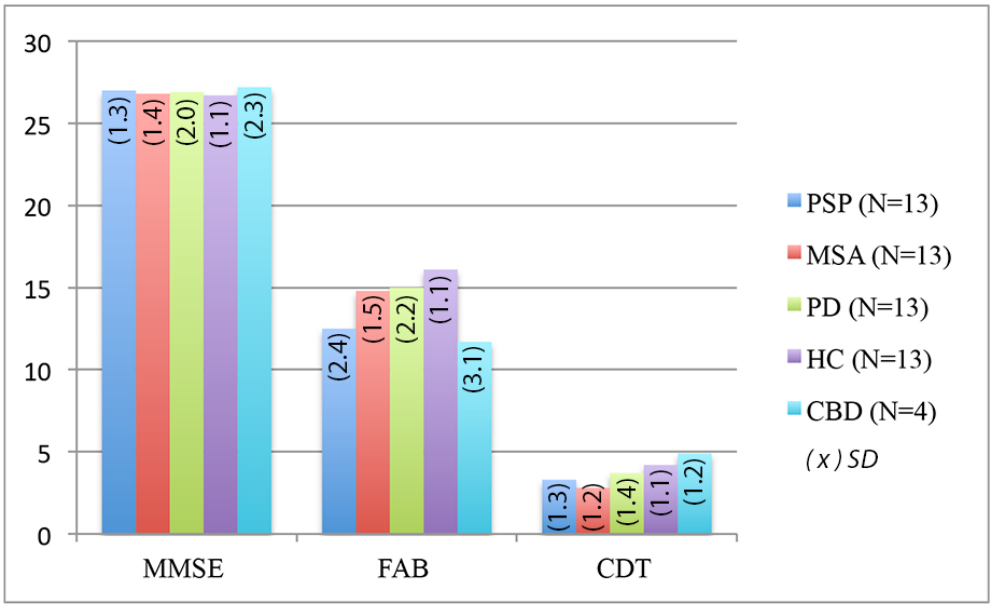


***Figure** 7: graph of the results on neuropsichological tests.*

Abbreviations: PSP, Progressive Supranuclear Palsy; MSA, Multiple System Atrophy; PD, Parkinson's Disease; HC, Healthy Controls; CBD, Cortico-Basal Degeneration; MMSE, Mini Mental State Examination; FAB, Frontal Assessment Battery; CDT, Clock Drawing Test.

As regards creativity (Table 3, Figure 2), we observed that, with exception of the comparison in fluency score between PSP and MSA, PSP patients were characterized by lower values in total ATTA and all subscales than HC and both MSA and PD

patients. No difference was found in CBD patients who also presented lower values than HC (P<0.05 for all scores).

Figure 8: *Divergent thinking features assesed by ATTA.*

Score	PSP M(SD)	MSA M(SD)	PD M(SD)	HC M(SD)	CBD M(SD)	P-value*	P-value§	P-value‡	P-value†
Fluency	7.3 (3.6)	9.7 (5.2)	11.5 (3.0)	12.9 (2.4)	8.5 (2.6)	0.24	0.005	0.001	0.49
Flexibility	5.1 (1.8)	7.7 (4.3)	9.5 (2.7)	10.5 (2.6)	5.8 (1.5)	0.037	<0.001	<0.001	0.48
Originality	5.8 (4.0)	10.5 (6.3)	15.1 (6.0)	14.7 (5.5)	5.3 (3.8)	0.016	<0.001	0.001	0.80
Elaboration	8.2 (5.6)	17.2 (15.7)	19.3 (9.5)	18.2 (8.6)	8.0 (3.5)	0.031	0.003	0.003	0.95
ATTA total	26.4 (12.6)	45.2 (28.5)	55.4 (18.2)	56.3 (16.8)	27.5 (10.2)	0.025	<0.001	<0.001	0.86

Abbreviations: PSP, Progressive Sopranuclear palsy; MSA, Multiple System Atrophy; PD, Parkinson's Disease; HC, Healthy Controls; CBD, Cortico-Basal Degeneration
* PSP vs. MSA by paired t-test
§ PSP vs. PD by paired t-test
‡ PSP vs. HC by paired t-test
† PSP vs. CBD by unpaired t-test

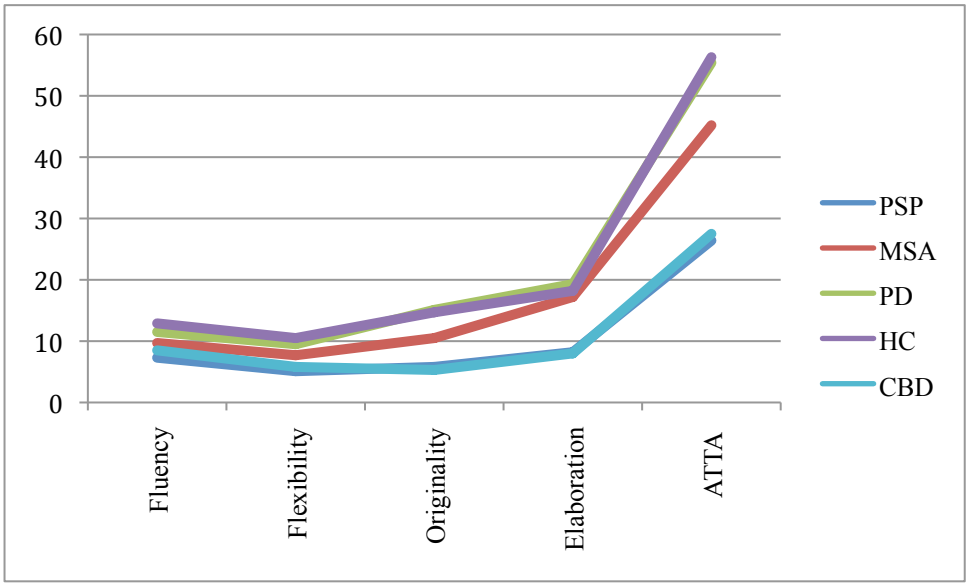


Figure 9: *graph of ATTA results.*

Abbreviations: PSP, Progressive Sopranuclear palsy; MSA, Multiple System Atrophy; PD, Parkinson's Disease; HC, Healthy Controls; CBD, Cortico-Basal Degeneration

5.5. Discussion and conclusion

In the present study, we showed that DT measured by means of ATTA is significantly lower in PSP patients when compared with the other study groups. The worst performances at ATTA-total showed in PSP group suggest a prominent role of frontal function in the creative processes. The better performances at DT tasks obtained in MSA and PD study groups endorse the link between creative functions and frontal area.

The connection between divergent thinking (DT) and frontal areas has already been emphasized by several previous studies.

Highly creative subjects showed bilateral frontal activation during DT task (Carlsson et al., 2000). Fink et al. (2006) found frontal alpha synchronization as a selective top-down inhibition process in HC during DT tasks by means of the analysis of electroencephalogram alpha band (Fink et al., 2006). Moreover creativity requires cognitive abilities linked to prefrontal regions of brain (Dietrich, 2004, Dietrich & Kanso, 2010). Another verified hypothesis was that training increases creativity via reorganized intercortical interactions (Kowatari et al., 2008).

Martindale et al. (1999) found that creative subjects had significantly more right- than left-hemisphere activity (pariety-temporal EEG), as opposed to low creative people on a creative task, but not on a non-creative task. Therefore, Hoppe & Kyle (1990) indicate that creative and healthy subjects tend to have free access to mutual interaction of both hemispheres without marked inhibitory or disinhibitory effects from either cerebral hemisphere.

Flaherty presents a three-factor anatomical model of human idea generation and creative drive, focusing on interactions between temporal lobes, frontal lobes and limbic system. Evidence is drawn from functional imaging, drug studies, and lesion analysis (Flaherty, 2005).

All patients included in the study were non-demented when evaluated by means of MMSE (inclusion criteria). Significant differences were observed among the group in frontal functions evaluated by means of FAB. PSP (and CBD) patients performed worse when compared to the other study groups. No differences were evident in PD, MSA and HC groups. CDT was significantly worse in MSA when compared to HC.

The central issue regarding the divergent thinking is the role of dopamine. The studies already carried do not agree about it. Some recognize the dopaminergic therapy as

engine of creativity (Inzelberg, 2013; Faust-Socher et al., 2014) while others recognize a secondary role (Canesi et al., 2015) . Moreover, the increased level of dopamine in frontal-subcortical area during DA therapy has been associated to creative thinking and specifically the mainly involved areas are medial prefrontal cortex, anterior cingulate cortex, limbic system, ventral striatal system (Kulisevski et al., 2009; Lopez-Pousa et al., 2012).

The fact remains that dopamine is definitely one of the main actors in the creative process. Patients included in our study are in dopaminergic therapy (DATh), except the HC group. By definition, the pathologies we included do not respond uniquely to this therapy. In fact, PD group has a greater response of 20%, the response of the MSA group is partially positive while the response for PSP and CBD is negative. In addition, the involvement of frontal areas in disease is different.

However, our study has some limitations. First of all is the low sample size, justified by the rarity of the diseases, in particular as regards the CBD. In the second place the different ages of the subjects (PD > PSP; MSA), due to the fact that we matched the patients depending on the severity of the disease. Finally, the battery of neuropsychological tests is not detailed. This choice was made to accommodate the fatigue of patients and difficulties in maintaining attention for prolonged periods of time.

The sample of subjects as follows, however, allowed us to speculate on divergent thinking with a very low influence of dopaminergic therapy. The results obtained confirm that the relationship between divergent thinking and dopaminergic therapy is not univocal. Therefore we can say that the dopaminergic circuit is not the only neural basis of creativity. In fact, although PSP patients received the worst scores, MSA and PD patients obtained comparable ATTA scores, not only among themselves but also with those of HC. Surely a future study with functional neuroimaging's aid will help us to better understand which structures are involved. With the obtained data we can confirm that a key role is played by the limbic system (Canesi et al., 2012). The involvement of the limbic system indicates that divergent thinking is closely related to emotions and hedonic reward. Only in predisposed people, this combination of factors determines the increase of creative thinking. (Canesi et al., 2012; Flaherty, 2011). We can also confirm that DT is not connected to impulsive behavior, infact none of the

subjects were ICD positives. The midbrain dopaminergic system seems to play a role. This circuit correlates with goal-motivated behaviors which are closely related to creative thinking (Flaherty, 2011), damaged system by definition in our patients.

6. APPENDIX A

Abbreviated Torrance Test for Adulds (ATTA)

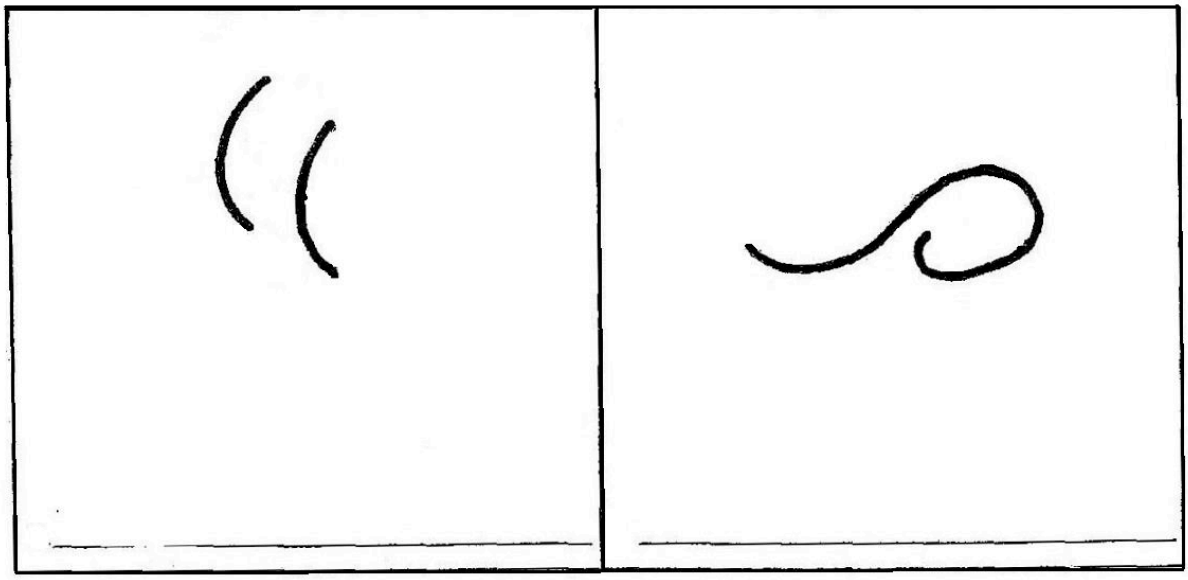
"Ora faremo alcune attività che richiederanno tutta l'immaginazione e l'abilità di pensiero possibile. Sono prove che vogliono vedere la capacità di usare l'immaginazione nell'escogitare idee e nell'esprimerle con parole o con disegni. Non ci saranno risposte giuste o sbagliate, diversamente dalla maggior parte delle cose che facciamo. Lo scopo è vedere quante idee le persone sono capaci di pensare. Cerchi di pensare a cose interessanti, insolite, estrose, qualcosa che nessun altro riuscirà a pensare. Per ciascuna attività ci sarà un limite di tempo, lavori più in fretta che può, ma senza precipitazione. Se esaurisce le idee prima che sia trascorso il tempo, può soffermarsi a pensare, potrebbero venirle altre idee ed aggiungerle."

PROVA NUMERO UNO: (VERBALE) PROVA A SUPPORRE

"Ora le presenterò una situazione improbabile, quindi una situazione che forse non potrà mai accadere. Deve provare a supporre che essa sia realmente accaduta. Ha la possibilità di usare tutta la sua immaginazione nel pensare a tutte le cose interessanti e emozionanti che accadrebbero SE questa situazione dovesse accadere realmente. Nella vostra immaginazione provate a supporre tutte le altre cose che accadrebbero in seguito a ciò. Fate il maggior numero possibile di ipotesi o supposizioni.
La situazione improbabile è la seguente: provate a supporre che attaccate alle nuvole ci siano delle corde che penzolano giù verso terra. Che cosa accadrebbe? Fate un elenco delle vostre idee e delle vostre supposizioni."

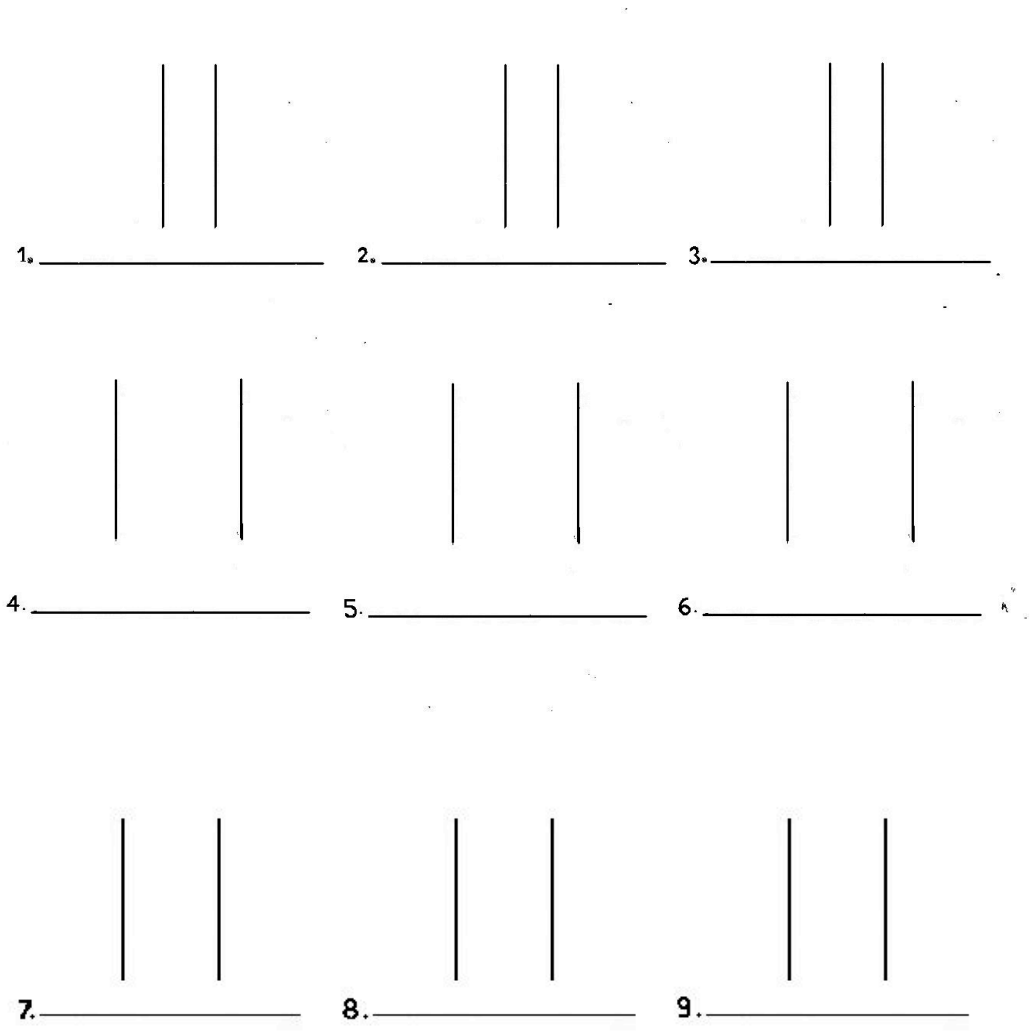
PROVA NUMERO DUE: COMPLETAMENTO DI FIGURE

"Aggiungendo altri segni alle figure incomplete di questa pagina, faccia degli oggetti o dei disegni interessanti. Cerchi di pensare a disegni e oggetti a cui non penserà nessun altro. Cerchi di far sì che ogni disegno racconti una storia quanto più completa e interessante, sviluppando la prima idea ed aggiungendo ad esse quante più cose vi è possibile. Per ciascun disegno inventi alla fine un titolo interessante, ingegnoso e insolito e lo scriva in basso."



PROVA NUMERO 3. LINEE

"In 5 minuti veda quanti oggetti o disegni può fare utilizzando le coppie di linee rette di questa pagina. Le coppie di rette dovranno essere la base principale di ciò che intende disegnare. Per completare il disegno, aggiunga dei segni alle coppie di linee con la matita, può fare segni dentro, fuori, in fianco alle linee purchè servano a completare il disegno.
Cerchi di pensare a cose a cui non penserà nessun altro. Cerchi di completare più disegni possibili, uno diverso dall'altro, con il maggior numero di idee possibile. Faccia in modo che i suoi disegni raccontino una storia quanto più completa possibile. Infine scriva un titolo sotto ad ogni disegno."



7. AKNOWLEGEMENTS

One word, worn, but shining like an old coin,
"Thank you!"
(Pablo Neruda)

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