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Cycle XXX

Apathy and Mood disorders after Acquired Brain Injury:

presentation of two research projects

FINAL PhD DISSERTATION

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To Mum and Gianluca,

my light and my strength,

because they have always believed in me.

To my patients,

because, sharing their stories, they

have allowed me to discover

the true value of life.

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List of Abbreviations

ABI	Acquired Brain Injury
ACC	Accuracy
AES	Apathy Evalutation Scale
ADRS	Aphasic Depression Rating Scale
ApABI	ABI patients with diagnosis of apathy
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
AD	Alzheimer's disease
CBT	Cognitive Behavioural Therapy
CES-D	Center of Epidemiological Studies-Depression Scale
CGI-S	Clinical Global Impression-Scale
CVA	Cerebrovascular accidents
DRS	Disability Rating Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
F-FT	Face-Flanker Task
GDS	Geriatric Depression Scale
GCS	Glasgow Coma Scale
GDB	Goal-directed behaviour
GHQ	General Health Questionnaire
GIP	Global Index of Performance
GOS	Glasgow Outcome Scale
GOS-E	Glasgow Outcome Scale-Extended
HADS	Hospital Anxiety and Depression Scale
H-FT	Hand-Flanker Task
L-FT	Flanker Task with letters
LCF	Levels of Cognitive Functioning
LIS	Locked-in Syndrome
MDD	Major depressive disorder
MCS	Minimally Conscious State
NPI	Neuropsychiatric Inventory
PFC	Prefrontal cortex

PHQ	Patient Health Questionnaire
PSA	Post Stroke Anxiety
PSD	Post Stroke Depression
PTSD	Post-Traumatic Stress Disorder
QoL	Quality of Life
RTs	Reaction Times
SADQ	Stroke Aphasic Depression Questionnaire
SoDS	Signs of Depression Scale
SSRIs	Selective Serotonin Reuptake Inhibitors
TAS-20	Toronto Alexithymia Scale-20
TBI	Traumatic Brain Injury
TIA	Transient Ischemic Attack
TMT_A	Trail Making Test A
VAMS	Visual Analogue Mood Scale
VASES	Visual Analogue Self Esteem Scale
VS	Vegetative State

Overview

I started my professional career as research psychologist in 2007 at the Post-Coma Unit of IRCSS Fondazione Santa Lucia in Rome, where I had the opportunity to be engaged in observational and multicentric studies on acquired brain injury patients and, more specifically, in translational clinical researches on patients with disturbance of consciousness. Furthermore, as clinical psychologist and psychotherapist, I provided psychological support (by means of group or individual psychotherapy) to family members of post-comatose patients hospitalized at the Post-Coma Unit.

I also worked at Headache Centre of IRCSS Fondazione Santa Lucia, mainly focusing my research activity on the study of mood disorders in chronic pain patients (in particular, with diagnosis of high-frequency migraine), and becoming member of the Italian Consensus Conference on Pain in Neurorehabilitation, an initiative of the Italian Society of Neurorehabilitation aimed at performing a critical appraisal of the scientific evidence on the role and the consideration of pain in the rehabilitation of neurological diseases.

Given my professional background and taking into account my strong interest in both acquired brain injury popolation and chronic pain patients, throughout my doctorate I focused my research activities on these important topics, in order to improve my scientific knowledge in these fields. I was involved in three different research projects: i) the study of apathy following acquired brain injury, using the Eriksen Flanker Task, ii) the preliminary validation in healthy subjects of the Hospital Anxiety and Depression Scale's visual form, in order to later assess the mood disorders in post-stroke aphasic patients, and iii) the study of the interdependence between emotions and pain perception in chronic headache patients. However, in this PhD thesis, I have only described and discussed the first two above mentioned research projects: even though they are completely different

each other (for aims, methodology, etc), they are both devoted to the investigation of motivation and mood-related alterations after acquired brain injuries.

Chapter 1 puts the emphasis on Acquired Brain Injury: definition, aetiology, disorders of consciousness (i.e., coma, vegetative state, and minimally conscious state), and outcomes have been widely discussed. More specifically, particular attention has been given to Traumatic Brain Injury, describing its mechanisms, neurobehavioral sequelae and neuropsychiatric disorders. Since behavioral alterations due to brain damage can also compromise and affect the well-being and quality of life of patients' caregivers (*Brain damage is a family affair*, as Lezak pointed out in 1988), an extensive description of the family burden, caregivers needs and their role changes has been provided.

Chapter 2 is focused on apathy, one of the most common behavioral consequences of acquired brain injury. Even though apathy is commonly noted, it is rarely investigated among this clinical population: it is often neglected in clinical practice and rehabilitation programmes are not targeted. Particular attention has been given in differentiating apathy from depression and in defining it according to the Levy and Dubois (2006) classification. The neuroanatomical correlates of apathy and its prevalence in the traumatic brain injury population have been also described.

Chapter 3 illustrates my first study where the main aim was to examine the possible relationship between apathy and conflict response in acquired brain injury patients diagnosed with apathy, compared to those without apathy and healthy controls, by using the three different types of flanker tasks (two of them realized for the specific purposes of this study). Indeed, very little is known in literature about the relationship between apathy and conflict monitoring, especially in acquired brain injury patients. On the other hand, different studies suggested that depression is associated with deficits in cognitive control, specifically those involved in conflict monitoring (Davidson et al., 2002; Vanderhasselt et

al., 2012; Clawson et al., 2013), since depression seems to be related to dysregulated interactions between specific brain areas involved in tasks requiring cognitive and attentional control.

Chapter 4 was thought to create a link with the last chapter, dedicated to the preliminary validation of a visual form of the Hospital Anxiety and Depression Scale to be administered to post-stroke patients who show both mood and language disorders. For this reason, this chapter is focused on the description of post-stroke mood disorders, such as depression, anxiety, post-traumatic stress disorders and pseudobulbar affect. Their treatment, both phamacological and non-pharmacological, has been broadly discussed.

Lastly, *Chapter 5* shows the second study I conducted during my PhD programme, which aimed to firstly realize a visual form of the Hospital Anxiety and Depression Scale, one of the most commonly used tool to assess mood disorders in clinical setting, and secondly, to administer it to a wide sample of healthy Italian individuals. More specifically, this study represents the first step of the validation process of the visual version of this scale, to study its reliability and equivalence with the original written form (Zigmond and Snaith, 1983), and implement a new visual tool able to assess anxiety and depression in post-stroke patients with severe language disorders (i.e. aphasia), which often represent an obstacle to detect the presence of mood disorders in this clinical population.

Chapter 1

Acquired Brain Injury

"I'm doing the best I can. My best may not what it was before my brain injury…but it's still the best I can.
I can not return to the person I once was… make sure you give yourself that time to mourn and accept the person you will become. Stay very hopeful and realistic".

(Antonio, 20 years old, a TBI survivor)

1.1.Definition

Acquired brain injury (ABI) embraces brain damage with different aetiologies, such as traumatic brain injury (TBI) (caused by motor vehicle accidents, falls, sports accidents, etc.) and cerebrovascular accidents (CVA), such as stroke or subarachnoid haemorrhage (Magee et al., 2017). It is an umbrella term which also includes aneurysms, brain tumors, vestibular dysfunction, and /or post-surgical complications resulting in anoxia or hypoxia (Juffreda and Kappor, 2012).

The Medical Disability Society (1988) defines ABI as severe when coma lasts at least 6 hours, while the definition of "prolonged coma" has been suggested as an indicator of "very severe brain injury" for patients with unconsciousness lasting at least 15 days (Danze, 1993; Formisano et al., 2004). Severe ABI is considered as the most common cause of death and disability worldwide, as it usually results in cognitive, physical, emotional or behavioral impairments that lead to permanent or temporary changes in functioning and can severely impact the survivor's quality of life (QoL) (Groher and Crary, 2010; Giustini et al., 2014; Formisano et al., 2017; Magee et al., 2017). The main

consequence of ABI is a dramatic change in the individual's daily life, which involves a disruption of the family, a loss of future income capacity and an increase of lifetime cost.

1.2 Disorders of consciousness

Severe ABI results in the dissolution of consciousness, defined as "a serially time-ordered, organized, restricted and reflective awareness of self and the environment" (James, 1894). Disorders of consciousness (DoC), including coma, vegetative state (VS), and minimally conscious state (MCS), exist on a continuum, and patients may or may not pass sequentially through each of these consciousness disorders.

Plum and Posner (1982) defined *coma* as a complete failure of the arousal system, with no spontaneous eyes opening in patients unable to be aroused by vigorous sensory stimulation, while the definition by Jennett (1986) includes the clinical triad of "closed eyes, not obeying simple commands, no comprehensible verbal utterances".

The most widely used scale in the acute phase (i.e. Intensive Care Unit) to assess the severity of coma after TBI, is the Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974) a 15-point scale which measures the motor, verbal and eye-opening response of the patient, providing an objective way of recording the conscious state and estimating the outcome of brain injury. Conversely, the Disability Rating Scale (DRS) (Rappaport et al., 1982), Levels of Cognitive Functioning (LCF) (Hagen et al., 1979), Glasgow Outcome Scale (GOS) (Jennett and Bond, 1975), and Glasgow Outcome Scale-Extended (GOS-E) (Jennett and MacMillan, 1981) are the most commonly used scales in the post-acute phase.

VS is a condition that follows coma when the patient recovers vigilance (eyes opening and partial recovery of the sleep-wake circadian cycle), but not awareness, defined as the ability to interact with the environment. Presently, the time interval potential for the recovery is one year for trauma cases and 3-6 months for all other etiologies.

Different complex neurological syndromes and comorbidities may affect the responsivity of the patients, such as undiagnosed epileptic activity (Vespa et al., 1999), parkinsonism (Formisano et al., 2009; Formisano et al., 2011a; Formisano and Zasler, 2014), or medical complications, as recurrent infections and fever. Furthermore, pathological postures in decortication (flexion and intrarotation of the upper limbs along with intrarotation and hyperextension of the lower limbs) (*Fig.1.1*) and decerebration (intrarotation and hyperextension of the upper and lower limbs) (*Fig.1.2*) often showed by DoC patients, may represent a negative indicator of long-term functional outcome (Dolce and Sazbon, 2002).

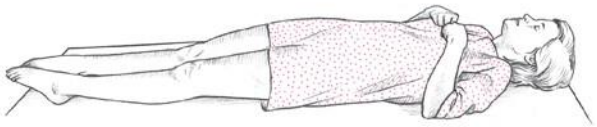

***Fig.1.1 Decorticate posture**. It results from damage to one or both corticalspinal tracts. The arms are adducted and flexed, with the wrists and the fingers flexed on the chest. The legs are stiffly extended and internally rotated, with plantar flexion of the feet.*

***Fig. 1.2 Decerebrate posture**. It results from damage to the upper brainstem. The arms are adducted and extended, with the wrists pronated and the fingers flexed. The legs are stiffly extended, with plantar flexion of the feet.*

Recently, the European task force has introduced the definition of Unresponsive Wakefulness Syndrome (UWS) (Laureys et al., 2010) to replace the term VS (which, in turn, had already substituted the terms “coma vigile” and “apallic syndrome”; Ashwal et al., 1994), although it has not been universally accepted (Formisano et al., 2011b).

An accurate differential diagnosis is crucial both for the correct clinical management of DoC patients, and to avoid misdiagnosis (i.e. diagnostic errors), since some studies have reported that up to 43% of DoC patients are erroneously assigned a diagnosis of VS (Schnakers et al., 2009). Indeed, the behavioral assessment of DoC patients may be compromised by different impairments, which prejudice the correct evaluation of the consciousness disorder. For instance, the presence of monolateral or bilateral ptosis may impair the patient's attempts at communication via eyelids closure, leading to possible diagnostic errors. Thus, differentiating VS from MCS remains one of the most challenging tasks for clinicians involved in the care of DoC patients.

MCS is defined by the presence of inconsistent but reproducible goal-directed behaviors (e.g. response to command, verbalizations, visual pursuit, etc.) (Giacino et al., 2002) and it may follow either coma or VS as transition or permanent condition.

Behavioral assessment remains the "gold standard" for detecting signs of consciousness and, hence, for determining diagnosis (Majerus et al., 2005) but, as already mentioned, the evaluation of the consciousness level is difficult and it may be affected by sensorial disorders (i.e. visual and auditory deficits), neuropsychological disorders, such as aphasia or apraxia, convulsive and nonconvulsive seizures (Vespa et al., 1999), psychomotor agitation, restlessness, aggressiveness, erratic behaviors (Formisano et al., 2005), and normotensive or hypertensive hydrocephalus (Missori et al., 2006).

MCS was recently subcategorized, based on the complexity of patients' behaviours, in MCS "Plus", when the patient shows high-level of behavioural responses (i.e., command following, intelligible verbalizations or non-functional communication), and in MCS "Minus", which descibes low-level behavioural responses (i.e., visual pursuit, localization of noxious stimulation or contingent behaviour such as appropriate smiling or crying to emotional stimuli) (Bruno et al., 2011). When the patient recovers the functional

communication, he/she may be diagnosed as emerged from MCS or exit-MCS (Bruno et al., 2011).

1.3 TBI: definition, mechanisms, neurobehavioral sequelae and neuropsychiatric disorders

About the deficits following ABI, the most of research has been performed in the areas of TBI and CVA, whose neurological deficits include altered cognition, affect, and/or sensorimotor abilities. While the period of natural recovery from ABI varies and is not always complete, recovery following TBI ranges from few months to 1 or 2 years after the trauma onset, depending upon the nature and the severity of the damage (Juffreda and Kappor, 2012).

TBI has been defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force" (Menon et al., 2010). Examples of external forces include rapid acceleration or deceleration of the brain, penetration of the brain by a foreign object, and exposure to forces associated with blasts.

A TBI can be "penetrating" or "closed", depending on if there was brain tissue exposition or not, and the central nervous system injuries are divided into primary or secondary (Schwarzbold et al., 2008).

Primary injuries are related to the tissue impairment which results directly from the impact forces, which tend to be maximal in brain areas that experience the highest angular acceleration or deceleration impact (superficial > deep and anterior > posterior) (McAllister, 2011). The effects of high-speed, long-duration acceleration or deceleration injuries are maximal on axonal projections and small blood vessels within and from the brain stem, the parasagittal white matter of the cerebrum, the corpus callosum, the grey-white junctions of the cerebral cortex (Meythaler et al., 2001), and especially at grey-white

junctions in the ventral and anterior frontal and temporal lobes (Biger, 2007). This type of inertial injury is usually described as DAI (*Fig.1.3*).

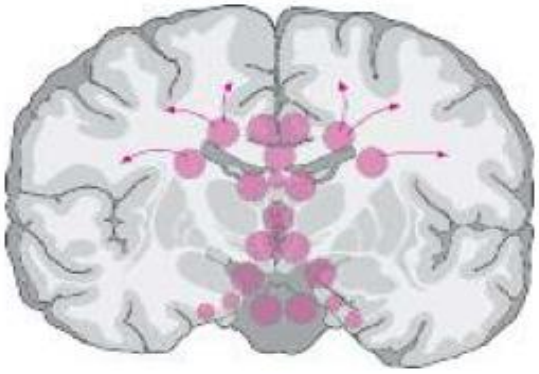

Fig.1.3 Diffuse Axonal Injury (DAI). *Damage occurs over a widespread area of the brain, in the form of micro and diffuse extensive lesions in white matter tracts*

Secondary injuries are developed subsequently as tissue response to the primary injuries (Bàrcena-Orbe et al., 2006), and some examples are inflammation, ischemia, glial proliferation (Nortje and Menon, 2004).

TBI is a worldwide public health problem. It has also been named "silent epidemic" because of the limited popular knowledge about the issue and of its symptoms, which may not be immediately evident (Schwarzbold et al., 2008). From 1 to 2 million cases occur each year in the United States (Rutland-Brown et al., 2006), while in Europe there is an annual incidence of 235 cases in 100,000 inhabitants (Tagliaferri et al., 2006). In the south of Europe, the main causes for TBI are traffic accidents, whereas falls, mainly related to alcohol use, are the major causes for TBI in the north of Europe (Tagliaferri et al., 2006). Almost 6.3 million people live with some level of disability, impairment or handicap related to TBI. In general, more than two thirds of the reported cases of TBI are mild, dividing equally the rest of them between moderate and severe ones (Tagliaferri et al., 2006).

Many individuals with TBI, particularly those with moderate and severe TBI, show significant long-term neurobehavioral sequelae and neuropsychiatric disorders (DHHS,

1989; Levin et al., 1990; Sorenson and Kraus, 1991). Neuropsychiatric symptoms, including disorders of cognition, mood, motivation, and behavior (Rao and Lyketsos, 2000; Ciurli et al. 2010) appear to have an important role in affecting long-term outcomes, particularly those related to independent living, social reintegration, family life, and return to work (Lippert-Gruener et al., 2002; Warriner et al., 2006).

Changes in cognition are the most common complaints after TBI (Lovell and Franzen,1994; Whyte et al., 1996): frontal executive functions (e.g. problem solving, impulse control, and self-monitoring), attention, short-term memory and learning, speech and language functions, and speed of information processing, are the cognitive domains typically impaired (Lehtonen et al., 2005; Rassovsky et al., 2006; O'Jile et al., 2006; Mathias and Wheaton, 2007).

Changes in personality are described as alterations in emotional and behavioral regulation after brain injury. In some individuals, personality change presents as amplification of preinjury traits, and it is important in this context to verify changes in the frequency and intensity of behaviors or traits that may have been present before the injury onset (McAllister, 2011). “Aggressive behavior” after TBI has been already highlighted as problematic and poorly understood (Prigatano, 1992; Kim et al, 2007). It is possible to classify aggression as impulsive behavior, consisting of verbal utterances, physical actions, snap decisions, and poor judgment flowing from the failure to fully consider the implications of a given action. Agitation, anger and irritability are often used as synonym terms (McAllister, 2011), even though impulsivity and anger seem to be the main characteristics of the aggressive behavior after TBI (Dyer et al., 2006), which is evidently disturbing in social life. Behavioral psychotherapeutic interventions can be useful (Baguley et al., 2006) as well the treatment of associated depression (Tateno et al., 2003). Preinjury aggressive behavior (Greve et al., 2001) and frontal lobe damage (Tateno et al., 2003) seem to be related to aggression after TBI.

Emotional instability, exaggerated emotional expressions, rapid mood changes are described as “affective lability”, phenomenon occurring in other central nervous system disorders and it is most likely related to disruption of “top-down” modulation of limbic responses to emotional stimuli by frontal cortex (Arciniegas et al., 2005). According to Arciniegas and coll. (2005) the affective lability is referred to an involuntary emotional expression disorder, in a continuum starting at a normal affective reaction, going through affective lability, and ending at pathological laughing or crying. Manifestations as laughing or crying episodes, which are excessive and represent a change in the previous emotional reactivity are the main features of the affective lability (Cunnings et al., 2006). Additional characteristics include a paroxysmal onset, brief duration, and subsequent remorse. Serotoninergic and dopaminergic drugs are pharmacological options (Rabins and Arciniegas, 2007), whereas a cognitive-behavioral intervention may be useful (Brooks, 2007).

“Apathy” has been classified as the milder extreme of the disorders of diminished motivation, a pathological spectrum which also includes abulia and akinetic mutism, in increasing order of severity (Schwarzbold et al., 2008). It can be of concern to family members and a barrier to progress in rehabilitation programs. It is often misinterpreted as laziness or depression, and it may be linked to aggression when individuals are pushed to be engaged in activities in which they have little interest (McAllister, 2000) Differently from apathy, depression is a dysphoric state and suffering is usually reported by patients, with a pessimistic view of themselves and the future (Marin and Wilkosz, 2005); it is also characterized by lack of interest, whereas apathy by lack of spontaneity (Prigatano, 1992).

Kant and coll. (1998) showed that apathy, associated to depressive symptoms, occurred in 60% of their sample of 83 TBI survivors, while Andersson and coll. (1999) found, among the 28 TBI subjects, that apathy prevalence reached 46,4%. Deficits in motivated behavior can occur in association with injury to the circuitry of “reward” (McAllister, 2000; Chau et

al., 2004). Cortico-striatal-pallidal-thalamic pathways (such as, anterior cingulate cortex, accumbens nucleus, ventral pallidum, and medial dorsal thalamic nucleus) are considered mediators of motivation. The orbitofrontal cortex, amygdala, hippocampus, and tegmental ventral area are also involved in the circuitry of reward related to the environment (Schwarzbold et al., 2008). Pharmacological treatments are able to improve motivation (Marin and Wilkosz, 2005), as well as psychological interventions addressed to increase the interest and the preserved communicative capacity of the apathetic patient can be useful (Schwarzbold et al., 2008).

Other personality changes include "behavioural disinhibition", characterized by the weak control of the impulses, a "paranoid type of personality", with suspiciousness and paranoid ideation as main features, and "self-awareness impairment" where, at the extreme level (anosognosia), patients are not able to recognize their acquired physical and neuropsychological deficits. "Disorders of self-awareness" (SA) are very frequent in TBI patients (Ben-Yishay et al., 1985; Bivona et al., 2008; Ciurli et al., 2010): they can cause low motivation for rehabilitation (Malec and Moessner, 2001) and interfere with safe and independent functioning (Flashman and McAllister, 2002), leading to poor outcome and difficulty in community integration and employability (Trudel et al., 1998; Sherer et al., 2003). SA, defined as the ability to recognize problems caused by damaged brain functions, has been divided into three main areas: "intellectual awareness" related to patients' ability to describe their deficits or impaired functioning; "emergent awareness", which regards patients' ability to recognize their difficulties as they are happening; and "anticipatory awareness", concerning patients' ability to predict when difficulties will arise because of their deficits (Crosson et al., 1989). According to Mathias and Wheaton (2007), TBI patients are less likely to be aware of changes in behavior and executive function than changes in more concrete domains, such as motor function.

In addition to the changes in cognition, behavior, and personality described above, a significant body of evidence suggests that TBI results in an increased risk of developing *psychiatric disorders*, including mood and anxiety disorders (Rapoport, 2010), sleep disorders (Vaishnavi et al., 2010), substance abuse, and psychotic syndromes (Hibbard et l., 1998; Koponen et al., 2002). With regard to mood disorders, depressive symptoms (Kreutzer et al., 2001; Kennedy et al., 2005; Kim et al., 2007), apathy (Marin et al., 1991; Marin and Wilkotsz, 2005; Kant et al., 1998) and anxiety are prevalent (Rao and Lyketsos, 2000); mania (Kim et al., 2007) and obsessive-compulsive disorder (Van Reekum et al., 1996) are reported less frequently. Psychosis, which is relatively rare, can also be a serious complication in TBI patients (Lippert-Gruener et al., 2002).

"Depression" is considered a common outcome in TBI survivors. Kim and coll. (2007) reported incidence rates of depression of 15.3 to 33% and prevalence rates of 18.5 to 61%. Many reasons for this wide variety can be mentioned. Firstly, depression is a multifactorial syndrome, since it is related to responses to stressing situations up to pathological conditions, and after a catastrophic injury, boundaries between depression, adjustment disorder and grief could become less demarcated (Rosenthal et al., 1998). Secondly, it could be difficult to distinguish depressive somatic manifestations from symptoms related to TBI or caused by other general conditions. Examples of overlapped symptoms are fatigue, insomnia, lack of concentration and appetite. About the brain areas account for depressive symptoms after TBI, it has been proposed that the rupture of neural circuits involving the prefrontal cortex, amygdala, hippocampus, basal ganglia, and thalamus may be related to the development of depression due to TBI. DAI and damage to the frontal and anterior temporal regions are frequent after TBI, and may explain the high rate of mood disorders among this clinical population (Jorge and Starkstein, 2005).

Different studies have revealed the influence of TBI severity and post-traumatic amnesia (PTA) on the epidemiology of *post-traumatic stress disorder* (PTSD) after TBI (Elbert and

Schauer, 2002). Gil and coll. (2005) found that subjects who had memories of the traumatic event within the first 24 hours were more likely to show PTSD. The occurrence of PTSD has been also reported after moderate and severe TBI, revealing that PTSD can occur even after severe TBI with extended PTA (Bombardier et al., 2006; Bryant et al., 2000). The identification of lesions in specific brain circuits in PTSD after TBI is still unclear. Sojka and coll. (2006) pointed out that the increase of the biochemical marker of brain tissue injury (the protein S-100B) in TBI acute phase, was related to the presence of PTSD one year later, observing the complex interaction between response to stress and brain tissue injuries.

Finally, several studies have raised a concern about the relationship of TBI to *dementia* (Van Den Heuvel et al., 2007), since amyloid precursor protein, A-beta, and other proteins associated with Alzheimer's disease (AD) and other neurodegenerative disorders accumulate rapidly after a TBI (Uryu et al., 2004, 2007; Chen et al., 2009). For instance, Mayeux and coll. (1995) retrospectively studied 113 older adults with AD, comparing them with a control group of 123 healthy older individuals, showing that the combination of APOE-e4 and history of TBI increased the risk of AD. However, not all studies have found such a relationship (Mehta et al., 1999). One possible explanation is that diminished cognitive reserve associated with TBI facilitates earlier manifestation of dementia symptoms in individuals already at risk for AD (Starkstein and Jorge, 2005). Therefore, although there are some compelling scientific reasons to consider the relationship of TBI to Alzheimer's disease and other neurodegenerative disorders, and some strong evidence suggesting clinical associations, the relationship between TBI and dementia needs further study.

To conclude, TBI is a significant public health problem because of both the high incidence of injury events and the high prevalence of chronic neurobehavioral sequelae, including cognitive deficits, personality changes and increased relative rates of psychiatric disorders

(particularly depression, anxiety, and PTSD), that can upset the lives of survivors and their family caregivers (*Table 1.1* and *Fig. 4*).

Neurobehavioral sequelae	Predominant brain regions involved
Cognitive deficits	
Working memory	Dorsolateral prefrontal, parietal, and cerebellar cortices; subcortical white matter
Short-term memory	Frontal and hippocampal cortices
Attention	Frontal, cingulate and parietal cortices, subcortical white matter, reticular activating system
Processing speed	Subcortical white matter tracts
Dysexecutive syndromes	
Disinhibition/social comportment	Orbitofrontal subcortical circuit
Cognitive dysexecutive	Dorsolateral prefrontal cortex
Disorders of motivated behavior	Medial frontal cortex, anterior cingulate, related reward circuitry
Psychiatric disorders	
Depression	?left anterior frontal cortex, temporo-limbic circuitry
Substance abuse	Components of reward circuitry (nucleus accumbens, frontal cortex)
PTSD	Medial and orbitofrontal cortices, amygdala, hippocampus

Table 1.1 Neurobehavioral sequelae and predominant brain regions involved. Neural substrates of common sequelae of TBI.

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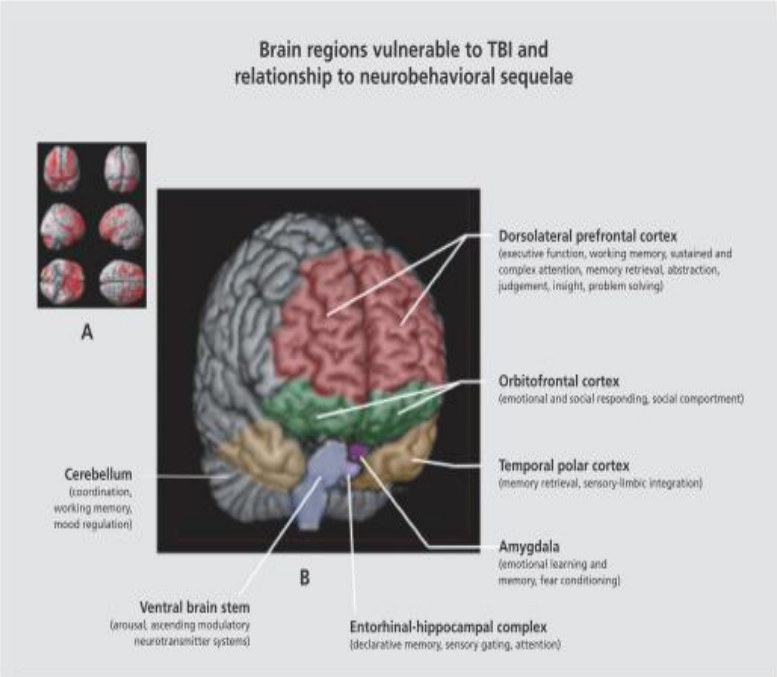

Fig. 1.4 (A) *Brain regions vulnerable to damage in TBI**; (B)*** *Relationship of vulnerable brain regions to common neurobehavioral sequelae associated with TBI.*
(A) *Adapted from ref 112: Bigler E. Structural imaging In: Silver J, McAllister T, Yudofsky S, eds. Textbook of Traumatic Brain Injury. Washington DC: American Psychiatric Press; 2005:87. Copyright © American Psychiatric Press, 2005.*
(B) *Adapted from ref 111: Arciniegas DB, Beresford TP. Neuropsychiatry: an introductory Approach. Cambridge, UK: Cambridge University Press; 2001:58. Copyright © Cambridge University Press, 2001*

1.4 Caring for the sABI patient: caregivers burden, needs and role changes

"I know pain. I know fear. I know tears. I know loneliness. I know confusion. I know the frustration. I know the loss of friends. I know the financial insecurity. I know the loss of Self. I know all these things, because I'm the caregiver of a TBI survivor".

(Eliana, 42 years old, a TBI caregiver)

The cognitive, emotional and behavioral changes of sABI patient can cause *family burden* (Perel et al., 2008; Kreutzer et al., 2009), defined as the extent to which caregivers feel that their emotional or physical health, social life and financial status have suffered as a result of caring for their relatives (Zarit et al., 1980). In fact, a large number of patients with sABI are supported by their family members, since they need continuous support and assistance in activities of daily living (Lancioni and Singh, 2014). Caregivers are often deeply involved in the patient's disease providing extraordinary and demanding care, and they often exhibit high rates of psychological distress, mood disorders, decreased QoL and

reduced personal independence (Verhaeghe et al., 2005; Rivera et al., 2007). They report putting themselves second to provide intensive support to the relative and, especially when the illness is in the critical phase, family members describe that their whole existence is focused on the patient, feeling a limitation on their personal freedom (Engrstöm and Söderberg, 2004; Őhman and Söderberg, 2004).

There is an ongoing issue about how carers define themselves (e.g. 'caregivers', 'parents' or 'supporters'), but this does not affect the indisputable strain of the role (Kuipers et al., 2010). An *informal caregiver* is defined as a person who, voluntary and without payment, provides care and support to someone in his/her family, or social network with physical, mental, or psychiatric disabilities (Spoorenberg et al., 2013). In particular, *primary* caregivers generally provide most of cares to the patient, and take most responsibility for the daily decisions, being engaged in different areas of assistance (e.g. personal care, financial assistance, housekeeping) (Sokolovsky, 1990) and becoming at greatest risk of poor psychosocial outcome (Perlesz et al., 2000); *secondary* caregivers do not have primary responsibility for the patient care (Scharlach et al., 2001), even though they may show high levels of psychological distress (Perlesz et al., 2000).

As Jennings (2006) noted, "the entire kinship system shakes" after a brain damage, and changes in relationship dynamics and family roles have been shown in some ABI studies (Serna and Sousa, 2006; Wongvatunyu and Porter, 2008). Indeed, post-injury perceived *role changes* are thought to be more problematic for spouses than parents (Chronister and Chan, 2006), since spouses often perceive a loss of role symmetry in their relationship, observing a change from being a romantic partner to assuming for example the role of parent, due to helping the loved one with personal care tasks, such as dressing and toileting. Also changes in sexual behaviors, often shown after sTBI (Kreuter et al., 1998; Moreno et al, 2013; Sander et al., 2013; Sander and Maestas, 2014), have a significant impact on the QoL of both TBI patients and their partners (Zasler et al., 1991; Turner et al.,

2015). Indeed, a recent study by Bivona and coll. (2016) revealed a reduction in desire and frequency of sexual intercourse in all male sTBI patients and their partners, and this reduced quality of sexual life seems to be more related to a relationship dysfunction than a sexual performance deficit due to the brain injury. In order to cope with post-injury changes, caregivers are asked to "renegotiate relationships", since the patient may often show a reduction, if not a total lack, to emotionally, intellectually or financially contribute to the relationship because of the deficit following the sABI.

However, even if such role changes are distressing for most of caregivers, others express their satisfaction in supporting and assisting their loved one. According to Kosciulek (1994), family adaptation to brain injury is defined as "the outcome of family efforts to bring a new level of balance, harmony, coherence, and a satisfactory level of functioning to a family following TBI", and Verhaeghe and coll. (2005) underlined that a better recovery is more likely when caregivers cope effectively with the TBI.

The pre-injury family dynamics and the caregivers' ability to access community resources (Adams and Dahdah, 2016), as well as *coping strategies*, such as acquisition of social support and resources, positive appraisal and family tension management (e.g. sharing problems with other family members, and taking a break from the care of patient) (Kosciulek, 1994), seem to be related to better outcome in caregivers. Furthermore, "emotion focused strategies", including acceptance, positive reappraisal, or seeking spiritual support, are positively linked to higher satisfaction of caregivers (Perlesz et al, 1999). However, coping strategies of caregivers are strictly related to their level of burden, distress and needs which, in turns, depend on the specific post-injury phase (Elbaum, 2007; Wells et al., 2005). Indeed, *family needs* may fluctuate and change over time (Rotondi et al., 2007): in the early phase (e.g., acute care and post-acute rehabilitation) the main caregivers' need is obtaining medical information on the patient, while a personal emotional support is required later, when they are no longer focused only on the patient's

necessities (Sinnakaruppan and Williams, 2001). Rotondi and coll. (2007) showed a modification of family needs throughout four phases, including acute phase, in-patient rehabilitation, the return to home and post-return home (i.e. living in the community). Understanding type, consequences and treatments of injury is the only common caregiver's need to these four phases. On the other hand, obtaining support from health professionals, family and friends and being involved in the rehabilitation program are the major needs in the post-acute rehabilitation and the return home, while the necessity to manage and plan their own life is typical of the living in the community phase (Rotondi et al., 2007).

Given the mutability of the caregivers' needs over time, it is very important to adjust the psychological intervention on the basis of the specific caregiver situation. Indeed, there is no yet a gold standard regarding the best approach to support sABI patients' caregivers in every setting, even though approaches including more interventions (e.g. educational methods, problem-solving techniques and psychological support) (Tverdov et al., 2016), as well as on-line psychoeducational support groups (Smith et al., 2012), seem to better take into account the individuality of caregivers instead of choosing a single intervention (Boschen et al., 2007), improving the family functioning.

In summary, family support is fundamental since the early stages of the patient's hospitalization, to bear the physical, social, and financial costs of the rehabilitation (Smith and Smith, 2000), and improve QoL of both sABI patients and their caregivers. However, the specific changes in lifestyle after the onset of a sABI have been poorly investigated in the literature, thus it could be interesting to explore how the caregivers' lifestyle changes in relation to the type and amount of assistance to the sABI patients.

Chapter 2

Apathy following Acquired Brain Injury

"Apathy is a sort of living oblivion".

(Horace Greeley)

2.1 Introduction

Apathetic manifestations are common across a wide variety of neurological and psychiatric conditions, such as TBI (Lane-Brown and Tate 2009), disorders involving the basal ganglia (Stuss et al. 2000; Pluck and Brown 2002), Alzheimer's disease (Fernandez Martinez et al. 2008) and CVA (Andersson et al. 1999b; Jorge et al. 2010). More pecifically, Arnould and coll. (2013), investigating the prevalence of apathy in TBI patients, revealed an overall point incidence of 47.3% of apathy across the studies they reviewed, while a study by Ciurli and coll. (2011) reported that TBI patients with a functional status recovery score indicating severe disability at the GOS had 4 times the risk of developing apathetic behaviors than TBI patients who have less severe scores.

Apathy is related to negative consequences both for the patients and their caregivers, in terms of poor recovery (Kant e tal., 1998; Hama et al., 2007), problems in daily functioning (Zahodne and Tremont, 2013), financial and vocational loss (Lane-Brown and Tate, 2009), lack of post-injury social reintegration (Mazaux et al., 1997), and caregiver distress (Willer et al., 2001). Yet, apathy is still a neglected neuropsychiatric syndrome in clinical practice, with no known standard treatment approaches and remains largely excluded from major psychiatric disease classification systems; on the other hand,

apathetic manifestations in TBI population often lead to more frequent and intensive consultations with healthcare centres and, therefore, represent a challenge to rehabilitation.

A potential source of confusion lies in the difficulty of clinically and conceptually differentiating apathy from depression.

Depression is defined, according to the World Health Organization's international classification of diseases, as a syndrome consisting in a permanent abnormal mood (at least for two consecutive weeks) and a marked diminished interest or pleasure and decreased energy associated to at least one of the following symptoms: loss of confidence, excessive guilt, recurrent thoughts of death, poor concentration, sleep disorders, and change in appetite or weight. Apathy is not a clinical criterion of depression but can be one of the clinical expressions of depressive state (Marin et al., 1993, 1994). The mechanisms by which depression induces apathy has not been totally clarified, even though it is very likely that apathy in depression results from an alteration of the emotional and affective processing via: (i) a marked sensitivity to emotionally negative situations inducing a negative bias interfering with attention resources and executive functions; or (ii) as the consequence of anhedonia (insensitivity to pleasure), which limits the will to perform actions.

In short, apathy is a symptom that can be observed in depression but may also occur without depression and, when both are present in a given patient they may be clinically and anatomically independent (Marin et al., 1994; Levy et al., 1998; Anderson et al., 1999; Kuzis et al., 1999).

Apathy is conventionally defined as an "absence or lack of feeling, emotion, interest or concern", and to clarify this concept for clinical purposes, Marin (1991, 1996) described it as "lack of motivation not attributable to diminished level of consciousness, cognitive impairment or emotional distress". However, apathy has been defined in different ways

(Lane-Brown and Tate 2009) and its underlying psychological processes are poorly understood.

In this perspective, I have considered the current definitions of apathy, its neuroanatomical correlates, and its prevalence in the TBI population.

2.2 Definitions of apathy

According to Marin (1991), apathy is a lack of motivation, characterized by *diminished goal-directed cognition* (as manifested by decreased interests, a lack of plans and goals, and a lack of concern about one's own health or functional status), *diminished goal-directed behaviour* (as manifested by a lack of effort, initiative and productivity) and *reduced emotional concomitants of goal-directed behaviours* (as manifested by flat affect, emotional indifference and restricted responses to important life events). Goal-directed behaviour (GDB) is defined as a set of related processes (motivational, emotional, cognitive and motor) by which an internal state is translated, through action, into the attainment of a goal (Schultz 1999; Brown and Pluck 2000), which can be immediate and physical, such as relieving thirst, or long-term and abstract, such as being successful in one's job or pursuing happiness.

Stuss and coll. (2000) argued that, since the assessment of motivation is problematic and requires inferences based on observations of affect or behaviour, apathy cannot be clinically defined as a lack of motivation (Marin, 1991), suggesting that it should be described as "an absence of responsiveness to stimuli—internal or external—as demonstrated by a lack of self-initiated action". Consequently, the construct of "initiation" is central to Stuss and colleagues' definition.

Other investigators emphasised that the absence of spontaneity observed among apathetic patients can be reverted under strong solicitation from the external environment, testifying to a contrast between a deep alteration of self-generated behaviors and a relative

preservation of externally driven ones. In consequence, Levy and Dubois (2006) defined apathy as the "quantitative reduction of self-generated voluntary and purposeful behaviors", describing it as a pathology of voluntary action or GDB, and the underlying mechanisms responsible for apathy may be seen as dysfunctions occurring at the level of elaboration, execution and control of GDB (Brown and Pluck, 2000). In line with Stuss et al. (2000), Levy and Dubois (2006) divided apathetic syndrome into three subtypes (emotional, cognitive and behavioural) but replaced the behavioural domain with the concept of auto-activation.

The *emotional-affective* subtype (Levy and Dubois, 2006) is referred to the inability to associate affective and emotional signals with ongoing and forthcoming behaviors. Any change in the linkage between emotion-affect and behavior may lead to apathy, either by reducing the willingness to perform actions (loss of will, loss of goals, emotional blunting) and maintain them to their completion or by diminishing one's ability to evaluate the consequences of future actions (Eslinger and Damasio, 1985). The emotional-affective subtype may typically be assessed in apathy scales by questions such as: "Does anything interest you?", "Are you concerned about your condition?", and "Are you interested in learning new things?" (Marin, 1991; Starkstein et al., 1993; Robert et al., 2002).

This form of apathy is due to of *orbital—medial prefrontal cortex* (PFC) lesions (Rosen et al., 2002; Boone et al., 2003), as manifested by a decreased impact of emotion and affect on ongoing or forthcoming behaviors. In patients with focal orbital and medial PFC lesions, there is evidence that the inability to accurately evaluate the consequences of their own choices and actions on an affective and emotional basis induces a quantitative decrease in GDB (Eslinger and Damasio, 1985; Bechara et al., 1994; Bechara et al., 2000). Sultzer and coll. (2013) also showed that affective apathy symptoms are associated with low metabolism in left medial temporal, right anterior temporal, and left inferior frontal cortex.

The *cognitive* apathy, also named *cognitive inertia*, (Levy and Dubois, 2006) is the deficit in coordinating thoughts and actions with intentions to support social GDB, resulting in an impairment of elaborating a set of actions. It is related to impairments of the executive functions requested to plan and carry out GDB, such as planning, working memory, and task switching.

Patients may be apathetic as a result of working memory and planning deficits, difficulty in generating new rules or strategies or in shifting from one mental and behavioral set to another. Specific cognitive tasks, such as the Wisconsin Card Sorting task (rule-finding, maintenance and set-shifting), the Tower of London task (planning) or the literal fluency task (self-activation of cognitive strategies), can be used to detect this cognitive inertia.

A reduction of GDB can be secondary to lesions of the *lateral PFC*, which is represented by the dorsolateral (BA 9/46), ventrolateral (12, 44, 45, 47) and frontopolar (lateral 10) regions (Goldman-Rakic, 1987; Fuster, 1997; Petrides and Pandya, 1999). In particular, impairments in planning, rule-finding, set-shifting, working memory and the self-activation of strategies for retrieval in declarative memory are often observed after lateral PFC lesions.

In particular, the cognitive apathy seems to be related to *lesions of the dorsolateral PFC*, associated with difficulties in activating mental strategies to generate rules, retrieve words or information from declarative memory, and in elaborating new patterns of behavior (it is like a dysexecutive syndrome). This loss of self-activation of cognitive strategies may quantitatively diminish motivation and impoverish behavior.

The *auto-activation* subtype, called “athymhormia” (Levy and Dubois, 2006), is referred to difficulties in activating thoughts or initiating the motor program necessary to complete the behavior. It consists in a loss of spontaneous activation that seems to affect both cognitive and emotional responses. Patients tend to remain quietly in the same place or position all day long, without speaking or taking any spontaneous initiative. When questioned, patients

express the feeling that their “mind is empty”. Affect is usually flattened with anhedonia and emotional responses are blunted; any reactivity to emotional situations is poor and shortlived. One of the most important features of this syndrome is that it can be temporarily reversed by external stimulation and, when solicited, patients can produce relevant answers and behaviors. In other words, there is a sharp contrast between the drastic quantitative reduction of self-generated actions and the normal production of behaviors in response to external solicitation. It can be assessed, in apathy scales, by questions contrasting self- and externally driven behaviors in activities of daily living such as ‘Does someone have to tell you what to do each day?’ ‘Do you need a push to get started on things?’ (Starkstein et al., 1992) and by the evidence of a severe spontaneous inertia that can be solicited by external cues in the absence of depressive mood.

This syndrome has been reported after focal *basal ganglia lesions* (Ali-Cherif et al., 1984; Habib and Poncet, 1988; Laplane et al., 1989; Starkstein et al., 1989; Bogousslavsky et al., 1991), in most cases affecting, bilaterally, the internal portion of the pallidum (Sawada et al., 1980; Klawans et al., 1982; Pulst et al., 1983; Laplane et al., 1984; Strub, 1989; Lugaresi et al., 1990). It may also occur after frontal lesions affecting the frontal deep white matter [close to the medial PFC (Laplane et al., 1988)]. Furthermore, Sultzer and coll. (2013) found that the auto-activation apathy symptoms are associated with low activity in bilateral insula.

The relationship between “auto-activation” deficit and some of the signs usually considered as “motor”, notably those referred to akinesia, (e.g. a diminished number of movements, delayed initiation and freezing), was questioned by Levy and Dubois (2006) who suggested that these ‘motor’ signs may arise from the same mechanisms leading to ‘auto-activation’ deficit, but in the domain of movement and gesture.

To conclude, there is some agreement within the literature that lack of interest, lack of initiative and emotional blunting are all dimensions of apathy and that diminished GDB is

at the core of the disorder (Marin, 1991; Levy and Dubois, 2006). Apathy is actually a multifaceted syndrome with distinct sub-domains, even though the majority of studies treat it as a unitary disorder (Levy and Czernecki, 2006; Robert et al., 2002; Marin, 1991).

2.3 Apathy prevalence after TBI and stroke

Changes in behavioural and emotional attitudes are common features described in persons with TBI, regardless of its severity (Arnould et al., 2016). These manifestations can be quite different (e.g.irritability, impulsity, apathy), and they often represent the biggest barrier to rehabilitiation in the acute phase as well as to reintegration into community on the long term (Meulemans et al, 2000). Furthermore, these behaviours are frequently associated to anosognosia which, in turn, makes care management and social, professional and familiar reintegration even more difficult.

Apathy was commonly described among the TBI population (Andersson and Bergedalen 2002; Lane-Brown and Tate 2009b), but despite its frequent occurrence and its negative impact on patients' functioning, it is rarely investigated among the TBI population.

Ciurli and coll. (2011) sought to characterize neurobehavioural changes among a group of 120 individuals with severe TBI. Using the Neuropsychiatric Inventory (NPI) (Cummings etal. 1994), the authors found that family caregivers reported a wide range of neuropsychiatric symptoms, underlying that apathy was shown by 42% of TBI patients, followed by irritability (37%), dysphoria/depressed mood (29%), disinhibition (28%), eating disturbances (27 %), and agitation/aggressive behaviour (24 %).

Apathy was studied in the TBI population using different scales such as the NPI, the Frontal Systems Behaviour Scale and the Apathy Evaluation Scale (AES): Arnould and coll. (2013) selected only studies whose main objective was to measure the prevalence of apathy or characterize neuropsychiatric disorders following TBI where the percentages of apathy were specified. Therefore, a total of 554 patients were assessed and 265 described

as apathetic,with an average prevalence rate of 47.83% (265 of 554).The lowest prevalence rate found in the studies was 20 % (Al-Adawi et al. 2004) and the highest was 72 % (Lane-Brown and Tate 2009) (see Table 2.1 from Arnould et al., 2013).

Author	Sample size	Injury severity	Time since injury (months)	Assessment instrument	Percentage of subjects with apathy
Van Zomeren and Van den Burg (1985)	57	Severe	24	Personal	23 %
Kant et al. (1998)	83	62 mild, 8 moderate, 9 severe	?	AES-S & AES-I (cut-off >34)	71.08 % (AES-S)
Marsh et al. (1998)	69	Severe	12.9 (±1.1)	Head Injury Behaviour Rating Scale (relative version)	Lack of motivation: 54 %, lack of initiative: 42 %
Andersson et al. (1999a)	30	Severe	10.5 (±1.68)	AES-C (cut-off >34)	66.7 %
Andersson et al. (1999b)	28	?	12.6 (±10.99)	AES-C (cut-off >34)	46.4 %
Andersson and Bergedalen (2002)	53	Severe	12.2 (±10.06)	AES-C (cut-off >34)	62.3 %
Al-Adawi et al. (2004)	80	6 mild, 2 moderate, 36 severe	8.35 (±4.50)	AES-S Arabic language version (cut-off >34)	20 %
Lane-Brown and Tate (2009)	34	Severe	80.58 (±71.64)	AES-I (cut-off >37) and FrSBe-A	AES-I: 69 % FrSBe-A: 72 %
Ciurli et al. (2011)	120	Severe	10.6 (±15.1)	Neuropsychiatric Inventory	42 %

Table 2.1 *Apathy prevalence rates in studies involving subjects with TBI.*
AES-C: Apathy Evaluation Scale- Clinician version; AES-I: Apathy Evaluation Scale- Informant version; AES-S: Apathy Evaluation Scale- Self report version; FrSBe-A: Frontal System Behaviour Scale-Apathy sub-scale; TBI: traumatic brain injury.

These findings indicated that apathy is a frequent symptom following TBI, but also highlighted the significant variation in prevalence rates, probably related to differences in the definition of apathy and the assessment tools. Indeed, it is still described and assessed in a number of different ways, with no instrument specially developed or thoroughly validated for the TBI population (Lane-Brown and Tate 2009). Although one might expect to find greater apathy among those with severe TBI, most studies did not report any correlation between apathy and the severity of the brain injury, as assessed by coma length, duration of post-traumatic amnesia or the GCS (Van Zomeren and Vanden Burg, 1985; Andersson et al. 1999a; Glenn et al. 2002; Andersson and Bergedalen 2002); age and education were also found to have no significant association with apathy among the TBI population (Van Reekum et al. 2005; Andersson and Bergedalen 2002). Some studies showed that apathy is more frequent or visible in the chronic phase than in the subacute

stage (Thomsen 1984; Van Zomeren and Van den Burg 1985; Kelly et al., 2008), whereas other studies found no significant correlation between time since injury and apathy score (Andersson et al. 1999a; Andersson and Bergedalen 2002; Lane-Brown and Tate, 2009). Furthermore, Kant and coll (1998) reported that younger patients were more likely to be apathetic than older patients, who were often both depressed and apathetic, while patients with severe injury were more likely to exhibit apathy alone.

Post-stroke apathy is a disabling symptom present in 20–55% of stroke survivors (Yamagata et al., 2004; Sagen et al., 2010; Withall et al., 2009, 2011) and it has been associated with post-stroke cognitive impairment, specifically with executive functioning impairment (Yamagata et al., 2004; Brodaty et al., 2005; Santa et al., 2008; Hommel et al., 2009; Mayo et al., 2009; Withall et al., 2011), even tough not all studies supported that association (Angelelli et al., 2004; Glodzik-Sobanska et al., 2005; Kaji et al., 2006; Sagen et al., 2010).

Some studies found that post-stroke apathy may be associated with post-stroke depression, but both can arise separately, while other studies showed an association between post-stroke apathy and poor functional outcome or inability to return to previous occupational and social activities (Brodaty et al., 2005; Hama et al., 2007; Santa et al., 2008; Mayo et al., 2009; Withall et al., 2009).

Chapter 3

The possible role of apathy on conflict monitoring: a behavioral study on severe acquired brain injury patients using Flanker tasks

- First study –

3.1 Introduction

As mentioned in the second chapter, the apathetic symptoms have been considered to partially overlap with depression, even though different studies have shown neuroanatomical and symptomatological differences between the two syndromes (Marin et al., 1994; Levy et al., 1998; Andersson et al., 1999).

Depression is associated with dysregulated interactions between: i) the rostral anterior cingulate cortex and dorsolateral prefrontal cortex, and ii) dorsolateral prefrontal cortex and dorsal anterior cingulate cortex, areas mainly involved in tasks requiring cognitive and attentional control. Individuale with major depressive disorder (MDD) also show functional and structural abnormalities in the rostral anterior cingulate cortex, dorsal anterior cingulate cortex, and dorsolateral prefrontal cortex (Pizzagalli, 2011). While a number of studies suggested that depression, in particular MDD, is associated with deficits in cognitive control, specifically those involved in conflict monitoring (Davidson et al., 2002; Vanderhasselt et al., 2012; Clawson et al., 2013), little is known about the relationship between apathy and conflict monitoring, especially in ABI patients.

Thus, in order to measure conflict monitoring and cognitive control in ABI patients with vs. those without apathy, we employed one of most widely used interference task: the Eriksen Flanker Task (Eriksen and Eriksen, 1974). It represents a recognized example of

this response conflict, where subjects have to respond to a central target flanked by distractors, usually letters or arrows. When the target and flankers are the same (congruent condition), reaction time is shorter and performance is more accurate than when the target is different from the flanker (incongruent condition) (Eriksen and Schultz, 1979).

Successful performance on this task, mainly on the incongruent condition, requires greater top–down cognitive control and a person's ability to suppress inappropriate or prepotent responses (Alderman et al, 2015), whereas unsuccessful performance has been reported in a number of clinical diseases such as schizophrenia, and substance use disorders and the above mentioned depression (van Veen and Carter, 2002; Pizzagalli, 2011).

In our study, we used three different flanker tasks: the classic flanker task (Eriksen and Eriksen, 1974), where target and distractors were formed by letters, and other two modified versions. As already mentioned, apathy can be divided into three subtypes: "emotional–affective", "cognitive" and "auto-activation", each related to different underlying disrupted mechanisms (Levy and Dubois, 2006). On these premises, our first modified task replaced the letters with emotional faces, while the second modified task substituted the letters with pictures of human hand postures having the index finger pointing to right or left, with a clenched fist. The modified emotional face flanker task may be linked to the emotional–affective subtype of apathy, while the flanker version with human hand postures could be associated to the auto-activation subtype, since we hypothesized that the hand image could have elicited the idea of action.

First aim of the present study was to examine the relationship between apathy and conflict response in ABI patients, diagnosed with apathy, compared to those without apathy and healthy controls, by using the three above described different flanker tasks. Although recognizing the lack literature concerning the conflict monitoring in ABI patients with diagnosis of apathy, we hypothesized that this clinical population would show deficit in conflict monitoring, both exhibiting a worse performance with respect to non apathetic

ABI patients and healthy controls, and showing a greater number of errors or missing responses.

Secondary aim of the study was to verify a possible correlation between the specific subtype of apathy (emotional–affective, cognitive, and auto-activation) and the type of flanker task ("cognitive apathy" vs. letter flanker task, "emotional–affective apathy" vs. emotional face flanker task and "auto-activation apathy" vs hand flanker task).

3.2 Methods

3.2.1 Participants

Twelve severe ABI outpatients with diagnosis of apathy (ApABI) were recruited at the Post-Coma Unit of the IRCCS Fondazione Santa Lucia of Rome. Ap ABI patients were included based on the following criteria: i) age ≥ 18 years; ii) diagnosis of severe ABI (Medical Disability Society, 1988); iii) LCF score ≥ 7 (Hagen et al., 1972); iv) time interval from head trauma longer than 6 months.

Participants were excluded from the sample in case of i) aphasia [score ≤ 29 in the Token Test) (De Renzi and Vignolo, 1962)] ii) any inability to undergo a formal psychometric assessment because of cognitive and/or severe sensory-motor deficits, iii) previous/current history of psychoactive drugs and/or alcohol consumption/abuse, or iv) previous history of psychiatric diseases and repeated ABI. Accordingly, 7 out of 12 participants were excluded (4 because of motor deficits, and 3 because of hemi-spatial neglect and diplopia), resulting in a *total sample* of *5* ApABI patients (3 males, mean age ± SD = 56.60 ± 12.05 years). The mean interval in months from injury to date of assessment (chronicity) was 60.4 ± 64.1. In addition, *5* severe ABI outpatients without diagnosis of apathy matched for age and gender (3 males, mean age ± SD = 58.60 ± 11.60 years) were enrolled as control group. Their chronicity in months was 34.8 ± 23.8. Although this interval was lower than ApABI patients, this difference was not statistically significant (p= 0.427, t-Test) (Table

3.1). In addition, 15 healthy participants (9 males, mean age ± SD = 54.46± 9.57 years) were enrolled as control group, having normal or corrected-to-normal vision and without any neurological or psychiatric diseases (Table 3.2). Age and education were compared among the three groups: no statistically significant differences were found for age (F=0.317, p=0.732), while significant differences were obtained for education (F=4.436, p=0.024).

Feature	**Parameter**	**ApABI (n.5)**	**ABI (n.5)**	**p-value**
Demographic and clinical features	Age (years)	56.6±12.1	58.6±11.5	0.690
	Aetiology (TBI/non TBI)	4/1	3/2	
	Education (years)	10.4±3.6	16.0±4.4	**0.019**
	Time since injury (months)	60.4±64.1	34.8±23.7	0.426
Abstract reasoning	Raven 36	29.5±3.2	30.8±2.0	0.291
Memory	Digit span forward	5.3±0.5	5.1±1.6	0.400
	Digit span backward	3.3±1.6	3.7±3.1	0.629
	Prose Memory Test	4.7±2.2	4.9±5.4	0.857
	Corsi Block-Tapping Test (span)	4.2±0.7	4.6±1.5	0.886
Attention	Trail Making Test A	87.5±39.5	44.4±18.6	**0.032**
	Trail Making Test B	281±92	142±95	0.063
Language	Phonemic Verbal Fluency test	12.2±8.3	25.3±21.0	0.999
	Semantic Verbal Fluency test	10.2±4.2	10.5±3.0	0.857
Executive functions	Frontal Assessment Battery	15.5±0.5	15.7±1.9	0.670
Depression	Beck Depression Inventory II	19.4±8.9	11.8±7.1	0.151

Table 3.1. *Ap ABI and ABI patients' clinical and demographical data.* Patients performances are expressed in mean and standard deviation of corrected scores. Pathological scores are in bold. P-values are obtained from Mann-Whitney u-test, in bold if statistically significant.

	Gender M/F	Age mean (s.d.)	Educational level mean (s.d.)
Ap ABI Patients	3/2	56,6 (12,5)	10,4 (3,36)
ABI Patients without apathy	3/2	58,6 (11,4)	16 (4,47)
Healthy Controls	9/6	54,4 (9,57)	13,6 (2,26)

Table 3.2. *Groups' characteristics.*

All patients underwent a neuropsychological assessment administered by a trained neuropsychologist, consisting in the following tests and batteries: i) Raven's Progressive Matrices (Basso et al, 1987); ii): forward and backward Digit Span Test (Orsini, 2003); iii) Corsi Block-Tapping Test (Orsini et al., 1987), iv) Prose Memory Test (Novelli et al., 1986); v) Frontal Assessment Battery-FAB (Apollonio, 2005), vi) Verbal Fluency Test (Novelli et al., 1986); vii) Trail Making Test A and B (TMT_A, TMT_B) (Reitan, 1958; Corrigan e Hinkeldey, 1987; Giovagnoli et al.1996) (see Table 3.1 above).

The diagnosis of apathy was assessed by first administering the clinician version of the Apathy Evaluation Scale (AES-C; Marin, 1996) to each patient and then the NPI (Cummings et al 1994) to each patient's caregiver (or family member). The AES-C is an 18-item instrument measuring apathy over the past 4 weeks and it is a reliable and valid measure of apathy following TBI, as it provides a multi-comprehensive picture of both the cognitive and emotional-affective dimensions of apathy (Lane-Brown and Tate, 2009). Each item, (e.g., s/he gets things done during the day) is rated on a scale of 1 (*Not at all characteristic*) to 4 (*A lot characteristic*) (see Appndix 1). To control for the possible influence of depression, the BDI (Beck et al., 1996) was also used to assess levels of depressive symptoms in the patient samples. Due to the complexity of the apathy

syndrome, it was difficult to distinguish the specific subtype of apathy exhibited by each patient: however, in our small sample, 2 patients were diagnosed as auto-activation apathy, 2 as emotional-affective and one as cognitive, even though 3 of these patients showed sympotms amenable to all apathy subdomains.

All patients also filled in the Toronto Alexithymia Scale-20 (TAS-20; Bagby et al., 1994a) to measure the alexithymia, described as impairment in identifying personal emotions. Its 20-item revised version comprises three factors: (i) difficulty identifying feelings; (ii) difficulty describing feelings; and (iii) externally oriented thinking.

Each participant provided written informed consent prior to their participation. The study was approved by the local Ethical Committee and conducted in accordance to the standards of the 2013 Declaration of Helsinki.

3.2.2 Stimuli

The experiment consisted of three different tasks, all of them inspired to the Flanker paradigm (Eriksen and Eriksen, 1974), but each defined by a specific set of stimuli (i.e., letters, human faces, and human hands).

The *Flanker Task with letters* (*L-FT;* Figure 3.1a) comprised white capital letters 'H' and 'S' as stimuli. Based on the nature of the Flanker paradigm (i.e., a target stimulus flanked by two bilateral distractors), there were 4 possible conditions: i) Congruent condition: same target and same flanker (2 stimuli: HHHHH and SSSSS) x ii) Incongruent condition: one target and one different flanker (2 stimuli: SSHSS and HHSHH).

The *Face-Flanker Task* (*F-FT;* Figure 3.1b), consisted in 2 different emotional face expressions (happy and sad) from the Karolinska Directed Emotional Faces database (KDEF; freely downloadable at http://www.emotionlab.se/resources/kdef; Goeleven et al., 2008). Eight types of face models were adopted: 4 male faces (2 happy and 2 sad) and 4 female faces (2 happy and 2 sad). Thus, the task consisted of 16 possible stimuli

combinations representing 4 conditions: i) Congruent condition (2 stimuli: 'happy target-happy flankers', and 'sad target-sad flankers'), and ii) Incongruent condition (2 stimuli: 'happy target-sad flankers', and 'sad target-happy flankers').

The *Hand-Flanker Task (H-FT;* Figure 3.1c) consisted of pictures of a hand posture (right- or left- pointing index finger with a clenched fist) of 4 subjects (2 males and 2 females). As for the F-FT, this task included 4 possible combinations: i) Congruent condition (2 stimuli: index finger to right as both target and flankers, index finger to left as target and flankers), and ii) Incongruent condition (2 stimuli: index finger to right as target, index finger to left as flankers, index finger to left as target, index finger to right as flankers).

Each size-class (307x105 pixels) stimulus (either a letter or a face or a hand) was presented on a black screen of a 15-inch computer monitor (1024×768 at 60 Hz), with a visual angle of 2° horizontally and 3,5° vertically. The visual angle between the center of the target and the center of each flanker was 0,5°. E-prime 2.0 (Psychology Software Tools) was used for stimulus presentation.

Figure 3.1. *Stimuli examples.* Figure 3.1a shows the stimulus example in the incongruent condition in L-FT; Figure 3.1b depicts the congruent condition in F-FT (happy target-happy flankers); Figure 3.1c displays the congruent condition in H-FT.

3.2.3 Procedure

Figure 3.2 depicts the timeline of the task. Participants sat on a comfortable chair in a quite and enlightened room, at a distance of ~56 cm from the computer monitor. At the beginning of each trial, a fixation cross ('+') was displayed for 600±50 ms before the stimulus (lasting 600 ms) simultaneously showing both target and the flankers. To decrease expectancy effects, the fixation cross varied randomly between 600 ms, 650 ms, and 550 ms, with a mean fixation cross duration of 600 ms.

Participants were asked to respond to the target (in the L-FT: 'H' or 'S'; in the F-FT: 'happy' or 'sad' face expression; in the H-FT: 'left-' or 'right-' pointing direction) as quickly and accurately as possible, by pressing the corresponding key of a computer-keyboard ('Q' or 'P') with their left- or right- index, respectively.

Each task (L-FT, F-FT, H-FT) consisted of a total of 480 trials, (120 presentations of each stimulus). The occurrence of congruent and incongruent stimuli was presented in a randomized order and was counterbalanced across trials (50%). To control for any effect of response habituation, participants performed sequentially two sessions of each task (each lasting 240 trials, 60 presentation of each stimulus), in which the stimulus-response mapping was inverted. The order of sessions was counterbalanced within subjects, while the order of tasks was counterbalanced across subjects.

Before undergoing each of the three tasks, participants performed a practice section of 32 trials (8 trials for each stimulus).

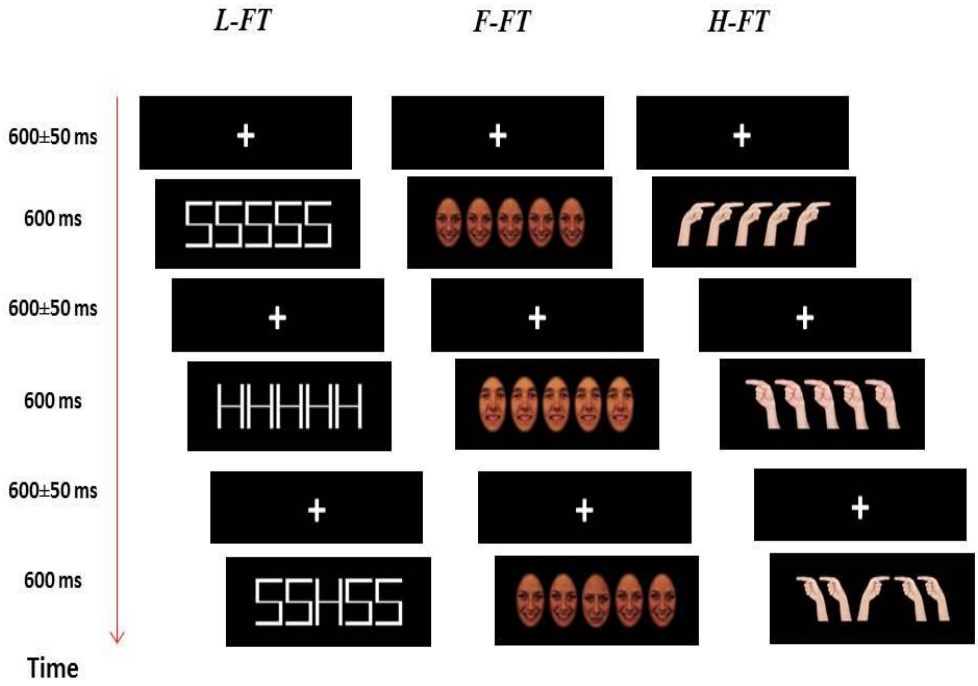

Figure 3.2. *Timeline of the task.*

3.2.4 Data analysis

Two measures of participants' performance were considered for each task, i.e. reaction times (RTs) and accuracy (ACC). RTs were defined as the time interval between the onset of stimuli and participant's button pressing. To control for outliers, trials were excluded if the response time was 2.5 standard deviations (SD) above or below the condition mean (<1 %). Moreover, trials were sorted according to the congruency of the stimuli presented (congruent vs. incongruent) and participants' response (correct vs. incorrect response), for each block and each participant, separately. RTs and ACC (in %) were derived before computing a global index of performance (GIP), defined as the Ratio between RTs (in ms) and ACC.

Data were firstly checked for normality (Shapiro-Wilk test) before computing parametric tests and post-hoc tests for multiple comparisons, from the General Liner Models. Mann-Whitney U-test were used to compare, between the groups of ABI patients, the demographic and clinical features.

RTs, ACC and GIP values were submitted to a Mixed Model Analysis of Variance (ANOVA) using Group as between-subject factor (3 levels: healthy subjects, ApABI patients, ABI patients without apathy), and both Task (3 levels: L-FT, F-FT, H-FT) and Congruency (2 levels: congruent vs. incongruent) as within-subject factors.

Effect size was estimated computing the partial eta squared ($\eta 2$). Post-hoc analyses were performed using Tukey's correction on p-values. For all the analyses the alpha-level for significant results were set at 0.05.

Furthermore, the performances of both groups of patients (ApABI and ABI) were compared to those of the control group (healthy subjects), by means of a single-case study (Crawford & Howell, 1998). Crawford and Howell's (1998) method has been widely used to test for acquired deficits in single-case research (Bird et al., 2004; Howard and Nickels, 2005; Papps et al., 2003; Robinson et al., 2005; Rosenbaum et al., 2005; Rusconi et al., 2006) in order to detect how a patient's score can depature from normality and to test the presence of deficit, regardless of the size of the control sample. In fact, Crawford and Howell's test allows to compare the patient's perfomance with a modestly sized matched control sample. We chose, as dependent variable, the difference of the GIP mean value between incongruent and congruent stimuli. These analyses were separately conducted for each task (L-FT, F-FT, H-FT). P-values were corrected using Bonferroni-Holm's procedure (Holm, 1979).

Finally, Spearman's rank correlation coefficient was used to assess the possible relationship between the subytype of apathy (cognitive, emotional–affective, and auto-

activation) and the performance of the apathetic patients to the 3 different tasks (L-FT, F-FT, H-FT).

3.3 Results

Clinical assessment of apathy resulted statistically significant among groups [$F(2,22)=124.06$, $p<0.001$, $\eta 2=0.919$], with significant lower scores for ApABI patients with respect to both healthy subjects and patients without apathy (post-hoc analysis: $p<0.001$ for both), without any statistically significant differences between these last two groups (values are reported in Table 3.3). Comparisons of other clinical parameters between the two patients groups showed statistically significant differences only for Trail Making Test A (TMT_A), that was in ApABI patients about twice that of ABI patients ($p=0.0317$). TMT_A was not found significantly correlated with apathy ($R=-0.609$, $p=0.082$): the only domain of apathy significantly related with TMT_A was the cognitive one ($R=-0.773$, $p=0.015$). No statistically significant difference was observed between the two groups of patients in the TAS-20 (Mann-Whitney u-test: $u=11$, $z=-0.313$, $p=0.754$), nor it was found statistically correlated with neuropsychological scores ($p >0.05$ for all clinical parameters).

Clinical assessment of apathy	**ApABI patients**	**ABI patients**	**Healthy subjects**	**p-value**
Apathy	35.8±0.8*§	59.8±4.3	62.2±3.4	**0.002**
Cognitive apathy	16.6±1.8*§	26.4±1.8	27.1±2.4	**0.002**
Emotional–affective apathy	9.6±1.3*§	17.4±1.8	17.3±1.0	**0.002**
Auto-activation apathy	4.6±0.9****	6.6±1.1	7.3±0.9	**0.003**

Table 3.3. *Assessment of apathy in ApABI and ABI patients, and healthy subjects.*
Data are reported in terms of mean and standard deviation and p-values refer to Kruskall Wallis analysis. Stars indicate a significant difference from healthy subjects, and § a significant difference from ApABI and ABI patients, all detected with post-hoc analysis (u-Test performed with Bonferroni correction). No differences were detected between ABI patients and healthy subjects.

3.3.1 Analysis on Performance (GIP)

Figure 3.3 shows the mean of GIP in all three groups of subjects, the three tasks and the two conditions. Higher values (i.e. worse performance) were observed in ApABI patients, in the F-FT task, and in the incongruent vs. congruent condition. A repeated measures ANOVA showed statistically significant main effect for Group [$F(2,22)=9.196$, $p=0.001$, $\eta 2=0.455$], Task [$F(2,44)=8.200$, $p=0.001$, $\eta 2=0.272$] and Congruency [$F(1,22)=8.172$, $p=0.009$, $\eta 2=0.271$], with lower values for congruent task. Post-hoc analyses performed on Group showed that only ApABI patients resulted in a significant difference from healthy subjects ($p<0.001$), whereas the performance of patients without apathy was not significantly different from that of healthy controls ($p=0.351$) who showed the better performance, as displayed in Figure 3.3. About Task, participants showed significantly better performances in the H-FT than in the F-FT ($p=0.009$). The interaction between Group and Congruency only approached the significant threshold [$F(2,44)=2.904$, $p=0.076$, $\eta 2=0.209$], whereas other interactions were even far from that. To deeply investigate these results, accuracy and RTs were also separately analyzed.

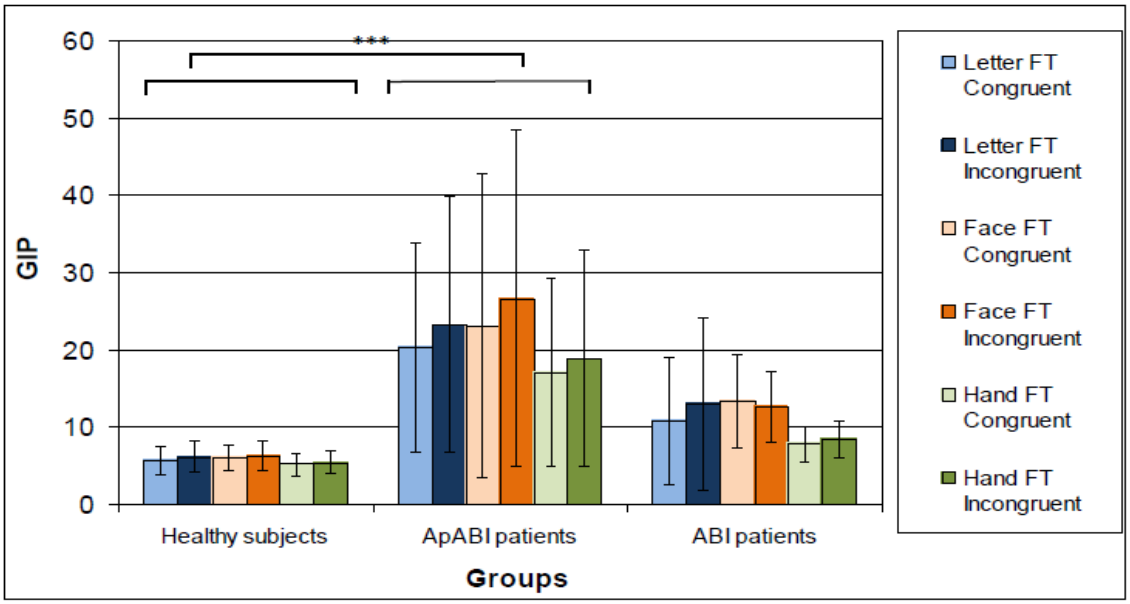

Figure 3.3. Mean of the GIP (higher values correspond to worse performance) in healthy subjects, ApABI and ABI patients for letters (blue), faces (orange) and hands (green) FT, in congruent (light color) and incongruent (dark color) trials.

3.3.2 Analysis on ACC

Mean values of ACC are displayed in Figure 3.4 where it is marked the higher accuracy of healthy subjects and the lowest of ApABI patients, together with the lower accuracy for incongruent trials vs. the congruent ones. The analysis on the ACC highlighted significant main effects of Group [F (2,22)=10.91, p=0.001, η2=0.498] and Congruency [F(1,22)=68.34, p<0.001, η2=0.756], with higher accuracy for congruent vs incongruent tasks. Post-hoc analyses revealed that healthy subjects had higher accuracy in comparison to both ABI patients with (p<0.001) and without (p=0.038) apathy (Figure 3.4). No interaction effects resulted from the analysis.

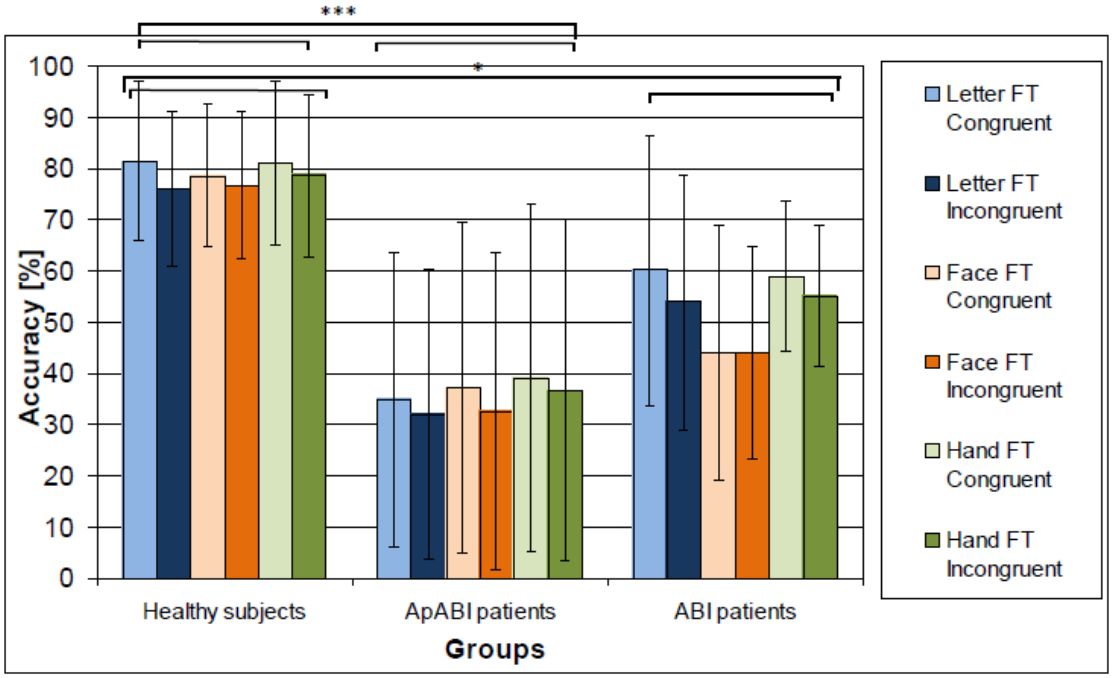

Figure 3.4. Mean of the ACC (higher values correspond to better accuracy) for healthy subjects, ApABI and ABI patients in the letters (blue), faces (orange) and hands (green) FT, and in congruent (light color) and incongruent (dark color) trials.

3.3.3 Analysis on RTs

Differently from previous results, slower response times were observed in ABI patients without apathy, who probably showed more effort to be accurate than apathetic ABI patients. About Task, faster RTs for H-FT in all the three groups were observed, as shown in Figure 3.5.

The analysis on RTs highlighted significant differences related to the Group [$F(2,22)=4.71$, $p=0.020$, $\eta2=0.300$], and Task [$F(2,44)=11.67$, $p<0.001$, $\eta2=0.347$]. Post-hoc analyses revealed that the group effects was related to slower RTs of ABI patients without apathy in comparison to both healthy subjects ($p=0.045$) and ApABI patients ($p=0.022$). No significant differences were noted between healthy subjects and ApABI patients ($p=0.592$) (Figure 3.5). As for Task, lower RTs (i.e. faster responses) in the H-FT with respect to both F-FT ($p<0.001$) and L-FT ($p<0.001$) were found.

Furthermore, post-hoc analyses showed that the difference found for the interaction Congruency x Group [$F(2,44)=4.06$, $p=0.032$, $\eta2=0.270$] was related to significant slower response time in the incongruent tasks of ABI patients without apathy in comparison to ApABI patients ($p=0.031$). No further interaction effects were found.

Slower RTs in ABI patients without apathy were found vs. those with apathy (especially for incongruent trials): this unexpected result could be related to the fact that response times were calculated without including missing trials, whose number was higher in ApABI patients than in non apathetic population (Ap ABI patients: *L-FT*, mean ± SD = 25.41 % ± 69.32; *F-FT*, mean ± SD = 25.00 % ± 70.88; *H-FT*, mean ± SD = 24.79% ± 74.06; ABI patients without apathy: *L-FT*, mean ± SD = 17.29 % ±53.32; *F-FT*, mean ± SD = 22.70 % ± 44.98; *H-FT*, mean ± SD = 11.45% ± 42.07; Healthy subjects: *L-FT*, mean ± SD = 6.60% ± 32.46; *F-FT*, mean ± SD = 6.60% ± 27.57; *H-FT*, mean ± SD = 5.41% ± 28.52~~)~~. To verify this hypothesis, a further analysis on missing trials was performed.

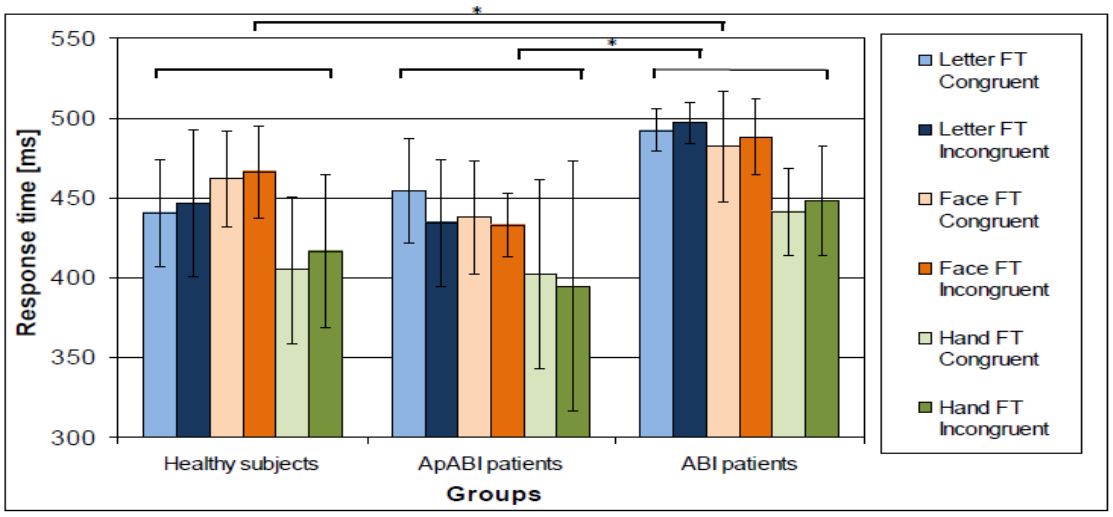

Figure 3.5 RTs mean (higher values correspond to slower responses) for healthy subjects, ApABI and ABI patients in the letters (blue), faces (orange) and hands (green) FT, in the congruent (light color) and incongruent (dark color) trials.

3.3.4 Analysis on Missing Trials

The number of missing trials was greatly higher in ApABI patients (mean: 120±69) than in healthy subjects (30±29), with the ABI patients positioned in the middle (82±51). This difference was statistically significant among Groups [F (2,22)=9.320, p=0.001, η^2=0.459]. Post-hoc analyses showed higher number of missing trials for ApABI patients in comparison to healthy subjects (p=0.001). Neither differences between patients with and without apathy (p=0.359), nor between healthy subjects and ABI patients without apathy (p=0.066) were statistically significant. Also Congruency [F (1,22)=51.334, p<0.001, η^2=0.700] and Task [F (2,44)=6.436, p=0.004, η^2=0.226] showed a statistically significant effect on missing trials: in particular, more missing for incongruent trials and face trials. Significant interaction effects were found for Group x Task (F(4,44)=3.845, p=0.009, η^2=0.259) and Congruence x Task (F(2,44)=3.289, p=0.047, η^2=0.130), whereas Group x Congruence (F(2,44)=2.989, p=0.071, η^2=0.241) and Group x Task x Congruence (F(4,44)=2.407 p=0.064, η^2=0.180) only approached the significant threshold (Figure 3.6).

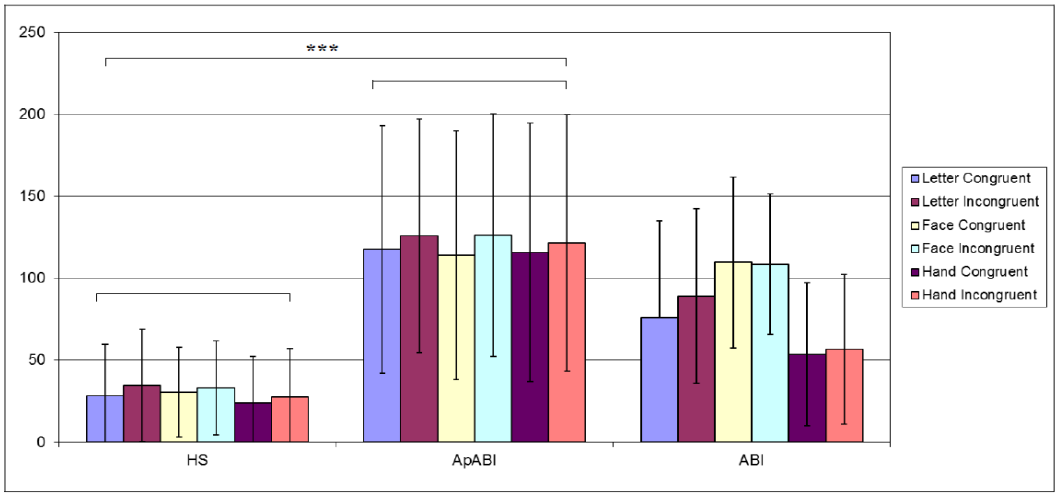

Figure 3.6. Number of missing trials in healthy subjects, ApABI and ABI patients for the L.FT, F-FFT, H-FT, and both congruent and incongruent trials.

3.3.5 Correlations with Apathy

A correlation between all the above analyzed parameters and the clinical assessment of apathy was tested. The total score of apathy was found significantly correlated with the ACC of L-FT incongruent trials (R=0.414, p=0.040), ACC of F-FT incongruent trials (R=0.443, p=0.026) and number of F-FT missing incongruent trials (R= -0.449, p=0.024). Other significant correlations were found, by dividing the apathy score in the three main subtypes (emotional–affective, cognitive, and auto-activation), as shown in Table 3.4. "Emotional-affective apathy" resulted transversally correlated with the subjects' GIP, since the subtype of apathy also influenced many other parameters such as: i) number of missing trials in the incongruent condition of L-FT (R= -0.472, p=0.017), in the congruent (R= -0.398, p=0.049) and incongruent conditions of F-FT (R= -0.495, p=0.012), in the congruent (R=0.462, p=0.020) and incongruent conditions of H-FT (R= -0.474, p=0.017); ii) ACC of F-FT incongruent trials (R=0.482, p=0.015), and of H-FT congruent (R=0.494, p=0.012) and H-FT incongruent trials (R=0.462, p=0.020); iii) RTs of F-FT incongruent trials (R=0.441, p=0.027).

GIP was found significantly correlated with the "auto-activation apathy" in the congruent trials of H-FT (R= -0.403, p=0.046). "Auto-activation apathy" was also related to number of missing trials in both congruent (R= -0.570, p=0.003) and incongruent condition of H-FT (R= -0.582, p=0.002).

"Cognitive apathy" was found significantly correlated only with ACC in F-FT incongruent trials (R=0.418, p=0.038). No other correlations were found between cognitive apathy and GIP (Table 3.4).

Type of task	**Congruent trials**			**Incongruent trials**		
GIP	**Letter FT**	**Face FT**	**Hand FT**	**Letter FT**	**Face FT**	**Hand FT**
Cognitive apathy	R=-0.318 p=0.058	R=-0.294 p=0.154	R=-0.252 p=0.224	R=-0.287 p=0.165	R=-0.363 p=0.075	R=-0.245 p=0.070
Emotional affective apathy	**R=-0.479 p=0.015**	R=-0.343 p=0.094	**R=-0.501 p=0.011**	**R=-0.407 p=0.044**	**R=-0.420 p=0.037**	**R=-0.468 p=0.018**
Auto-activation apathy	R=-0.344 p=0.092	R=-0.300 p=0.145	**R=-0.403 p=0.046**	R=-0.370 p=0.069	R=-0.301 p=0.144	R=-0.382 p=0.059

Table 3.4. Spearman's Correlation coefficient (R) and relevant p-values computed between clinical assessment of apathy of all subjects and their task performance (GIP), both in congruent and incongruent trials. Values are reported in bold if statistically significant. The grey cells of table graphically show the secondary hypothesis of this study: to find correlations between the subtype of apathy and its related task.

To follow the same logic proposed for the single case analysis showed below, correlations have been also conducted on the difference of the GIP mean value between incongruent and congruent stimuli.

In this case, "emotional-affective apathy" resulted higly correlated with the subjects' GIP in F-FT, suggesting that the more severe is the presence of this subtype of apathy (i.e. lower scores in the AES), the higher is the difference of the GIP mean value between incongruent and congruent stimuli in the F-FT.

Type of task	Difference between Incongruent - Congruent Trials		
GIP	**Letter FT**	**Face FT**	**Hand FT**
Cognitive apathy	R=0.341 p=0.334	R=-0.512 p=0.130	R=-0.189 p=0.601
Emotional affective apathy	R=-0.118 p=0.746	**R=-0.904** **p<0.001**	R=0.111 p=0.759
Auto-activation apathy	R=-0.012 p=0.973	**R=-0.636** **p=0.048**	R=-0.006 p=0.987

Table 3.5. Spearman's Correlation coefficient (R) and relevant p-values computed between clinical assessment of apathy of all subjects and their task performance (GIP), explained as difference between GIP mean value of incongruent stimuli and that of congruent stimuli . Values are reported in bold if statistically significant. The grey cells of table graphically show the secondary hypothesis of this study: to find correlations between the subtype of apathy and its related task.

3.3.6 Single case study

As for the L-FT, only one ABI patient whitout apathy reported a GIP Incongruent – GIP congruent difference that exceeded the upper limit of the 95% confidence interval of the control group (*Subiect 23*, Crawford-Howell t-test = 9.218, p < .001 Bonferroni-Holm corrected), as well as 2 ApABI patients (*Subiect 18*, Crawford-Howell t-test = 5.627, p < .001 Bonferroni-Holm corrected; *Subiect 20*, Crawford-Howell t-test = 19.897, p < .001 Bonferroni-Holm corrected), whereas other 2 patients with apathy reported an inverse effect, obtaining a value fell below the 95% confidence interval of the control group (*Subiect 16*, Crawford-Howell t-test = 7.640, p <.001 Bonferroni-Holm corrected; *Subiect 19*, Crawford-Howell t-test = 11.781, p < .001 Bonferroni-Holm corrected) (Table 3.6; Figure 3.7). These findings may suggest that ABI patients with and without apathy that exceeded the 95% confidence interval of the control group, were those obtained GIP higher scores (i.e. worse performance) in the incongruent trials of L-FT and, thus, they could be more influenced by the flanker effect. Conversely, the 2 patients with apathy with mean values below the interval confidence of the control group, were those with GIP higher

scores in the congruent trials of L-FT and, consequently, they were less influenced by the conflict produced by flankers stimuli.

	statistic	dof	p	ES	Group	p.adj	
Subj16	7.640	14	**0.000**	-9.488	Ap ABI	0.000	***
Subj17	1.740	14	0.104	-1.945	Ap ABI	0.519	
Subj18	5.627	14	**0.000**	6.660	Ap ABI	0.000	***
Subj19	11.781	14	**0.000**	-16.528	Ap ABI	0.000	***
Subj20	19.897	14	**0.000**	36.307	Ap ABI	0.000	***
Subj21	0.099	14	0.923	-0.109	ABI	1.000	
Subj22	1.327	14	0.206	1.479	ABI	0.823	
Subj23	9.218	14	**0.000**	11.959	ABI	0.000	***
Subj24	0.971	14	0.348	1.080	ABI	1.000	
Subj25	0.133	14	0.896	-0.148	ABI	1.000	

Table 3.6. Patients' performance, in L-FT, was compared with that of healthy control subjects by using the Crawford-Howell t-test for differences between incongruent and congruent stimuli. Dof= degree of freedom; ES= effect size.

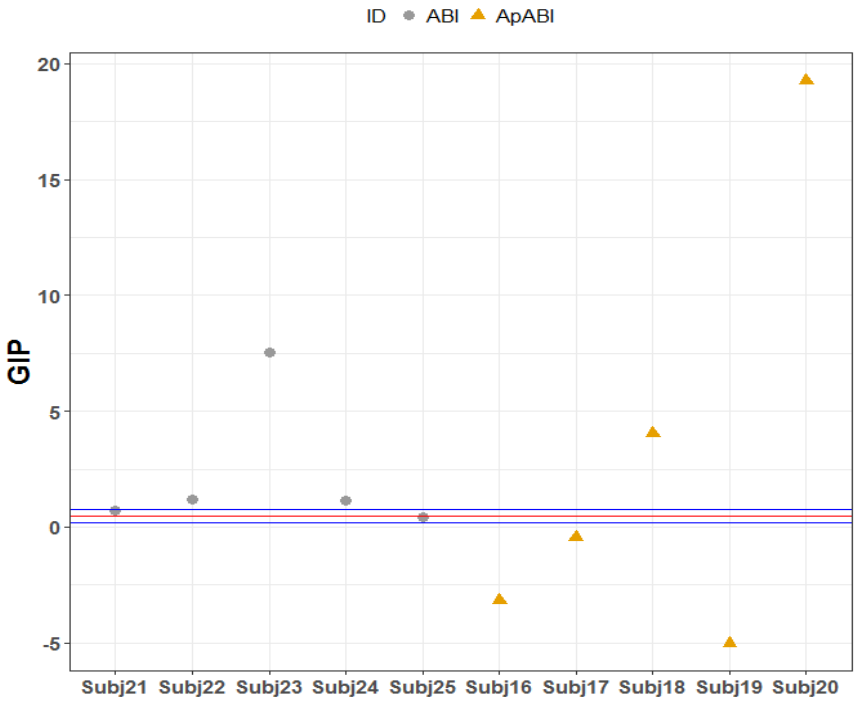

Figure 3.7. L-FT: GIP mean value of the difference between incongruent and congruent stimuli of each ABI patient, distributed above, below or within the 95% confidence interval of control group.
Red line= GIP mean value of the difference between incongruent and congruent stimuli of the control group; Blue line= confidence limits, the two extreme values of the confidence interval which define the range.

About F-FT, 3 ABI patients without diagnosis of apathy fell below the confidence interval of the control group (*Subject 21*, Crawford-Howell t-test = 11.99, p < .001 Bonferroni-Holm corrected; *Subject 22*, Crawford-Howell t-test = 4.984, p < .01 Bonferroni-Holm corrected; *Subject 23*, Crawford-Howell t-test = 7.841, p < .001 Bonferroni-Holm corrected), since their GIP value due to the difference between GIP values of incongruent and congruent stimuli, suggests a better perfomance in the incongruent trials (i.e. lower scores) in comparison to the congruent ones. Conversely, in the ApABI sample, 3 patients were above the 95% confidence interval of the control group (*Subject 16*, Crawford-Howell t-test = 4.679, p < .01 Bonferroni-Holm corrected; *Subject 19*, Crawford-Howell t-test = 12.147, p < .001 Bonferroni-Holm corrected*; Subject 20*, Crawford-Howell t-test = 14.444, p < .001 Bonferroni-Holm corrected) (Table 3.7; Figure 3.8).

	statistic	dof	p	ES	Group	p.adj	
Subj16	4.679	14	**0.000**	5.439	Ap ABI	0.002	**
Subj17	0.354	14	0.729	0.393	Ap ABI	0.945	
Subj18	2.103	14	0.054	2.359	Ap ABI	0.216	
Subj19	12.147	14	**0.000**	-17.286	Ap ABI	0.000	***
Subj20	14.444	14	**0.000**	22.154	Ap ABI	0.000	***
Subj21	11.909	14	**0.000**	-16.817	ABI	0.000	***
Subj22	4.984	14	**0.000**	-5.827	ABI	0.001	**
Subj23	7.841	14	**0.000**	-9.805	ABI	0.000	***
Subj24	0.772	14	0.453	0.859	ABI	0.945	
Subj25	1.042	14	0.315	1.160	ABI	0.945	

Table 3.7. Patients' performance, in F-FT, was compared with that of healthy control subjects by using the Crawford-Howell t-test for differences between incongruent and congruent stimuli. Dof= degree of freedom; ES= effect size.

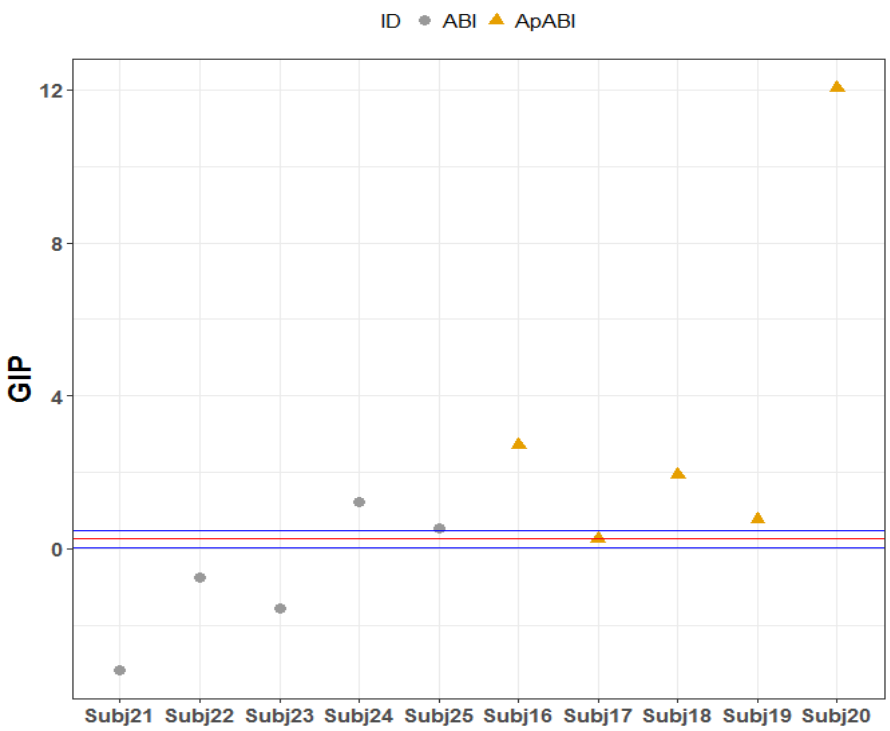

Figure 3.8. F-FT: GIP mean value of the difference between incongruent and congruent stimuli of each ABI patient, distributed above, below or within the 95% confidence interval of control group.
Red line= GIP mean value of the difference between incongruent and congruent stimuli of the control group; Blue line= confidence limits, the two extreme values of the confidence interval which define the range.

Finally, in the H-FT, only one ABI patient without apathy showed a GIP Incongruent – GIP congruent difference placed above the confidence interval of the healthy control group (*Subject 21*, Crawford-Howell t-test = 4.167, $p < .01$ Bonferroni-Holm corrected), as well as 2 ApABI patients (*Subject 16*, Crawford-Howell t-test = 8.954, $p < .001$ Bonferroni-Holm corrected and *Subject 19*, Crawford-Howell t-test = 10.474, $p < .001$ Bonferroni-Holm corrected). One ApABI also reported an inverse effect, obtaining a value fell below the 95% confidence interval of the control group (*Subject 18*, Crawford-Howell t-test = 3.403, $p < .05$ Bonferroni-Holm corrected), and suggesting the presence of GIP higher scores (i.e. worse performance) in the congruent trials of H-FT and, consequently, a reduced flanker interference (Table 3.8, Figure 3.9).

	statistic	dof	p	ES	Group	p.adj	
Subj16	8.954	14	**0.000**	11.548	Ap ABI	0.000	***
Subj17	0.744	14	0.469	-0.828	Ap ABI	1.000	
Subj18	3.403	14	**0.004**	-3.874	Ap ABI	0.030	*
Subj19	10.474	14	**0.000**	14.136	Ap ABI	0.000	***
Subj20	0.279	14	0.784	-0.310	Ap ABI	1.000	
Subj21	4.167	14	**0.001**	4.801	ABI	0.008	**
Subj22	0.444	14	0.664	-0.494	ABI	1.000	
Subj23	0.173	14	0.865	0.192	ABI	1.000	
Subj24	1.026	14	0.322	-1.142	ABI	1.000	
Subj25	1.289	14	0.218	1.437	ABI	1.000	

Table 3.8. Patients' performance, in H-FT, was compared with that of healthy control subjects by using the Crawford-Howell t-test for differences between incongruent and congruent stimuli. Dof= degree of freedom; ES= Effect size.

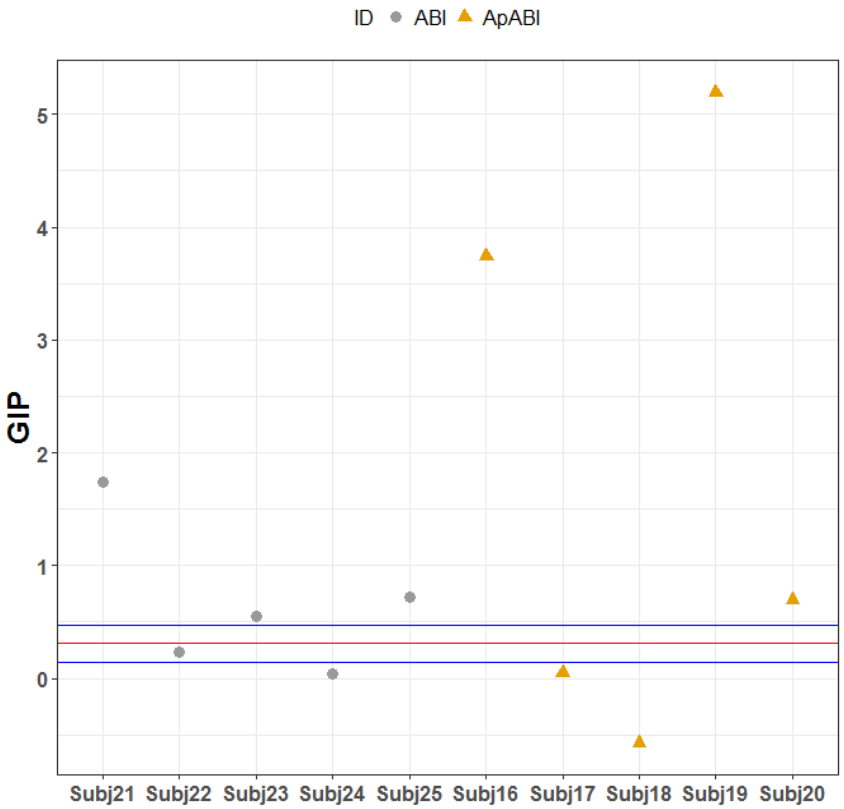

Figure 3.9. H-FT: GIP mean value of the difference between incongruent and congruent stimuli of each ABI patient, distributed above, below or within the 95% confidence interval of control group.
Red line= GIP mean value of the difference between incongruent and congruent stimuli of the control group; Blue line= confidence limits, the two extreme values of the confidence interval which define the range.

3.4 Discussion

Aims of this study were to investigate the relationship between apathy and conflict monitoring in ApABI patients, compared to those without apathy and healthy controls, by means of three different Flanker tasks, as well as to verify a possible correlation between the specific sub-domain of apathy and the type of task realized for the purpose of this study.

Very little is known about the potential influence of apathy on cognitive control (more specifically on conflict monitoring) and their relationship is still controversial. According to Andersson and Bergedalen (2002) there was a significant association between more severe apathy and executive dysfunction, as well as different studies have found an association between apathy symptoms and poor performance on standard executive function tests (Drijgers et al., 2011; Kuzis et al., 1999). For these reasons, apathy is frequently conceptualized as a "dysexecutive syndrome" (Mesulum, 2012). However, some studies have revealed inconsistent results on the relationship between apathy and executive deficits, suggesting that executive function deficits are not crucial for the presence of apathy symptoms (Njomboro et al., 2012; Njomboro and Humphreys, 2006).

One of the typical "interference" paradigm used to measure executive control and examine conflict monitoring is the Flanker task (Eriksen and Eriksen, 1974): some versions of it exist, even though they share the same structure where participants have to recognize the centrally presented stimulus flanked by two bilateral distractors, which can appear either identical to the target (congruent condition) or different from it (incongruent condition). Usually, RTs are slower and ACC is lower in the incongruent condition because of interference related to the confusing flankers (Dillon et al., 2015).

The main result of our study is that the performance (GIP) of ApABI patients was worse than that of healthy subjects, mainly in the incongruent trials, whereas that of ABI patients without apathy was not. Indeed, as single-case analysis pointed out, ApABI patients were

more influenced by flanker conflict in comparison to patients without apathy, whose performance, in some cases, fell within the confidence interval of healthy control group. This result supported the notion that apathy, like anxiety and depression, can directly impact cognitive performance, in particular that related to conflict monitoring, masking the subject's true ability (Geldmacher et al., 2012).

Conversely, the average response time of ApABI patients was not slower than that of patients without apathy, as expected. This result is probably due to the fact that for the computation of RTs, missing trials were not included while, on the contrary, they were calculated in the ACC computation. In fact, only ApABI patients showed a significantly higher number of missing trials in comparison to healthy subjects, whereas patients without apathy did not; furthermore, the number of correct responses provided by ApABI patients was significantly lower than both healthy subjects and ABI patients without apathy. The significant interaction Group per Task also revealed that ApABI patients exhibited a higher number of missing responses in the F-FT, suggesting that this clinical population presented more difficulties in recognizing emotional face expressions than non apathetic ABI patients and healthy participants. In fact, as highlighted by Njmboro and Deb (2014), the emotion recognition is usually impaired in patients with apathy.

These first results could support the main hypothesis of the study that ApABI patients may have had more difficulties in identifying the target stimuli, especially when target and distractors were facial emotion expressions, preferring a strategy of not reacting when they found more difficulties instead of taking more time to response. However, the 600 ms temporal window given to participants did not allow us to correctly evaluate if they responded after the target disappeared or failed to react to the stimulus, making errors of omission.

The secondary hypothesis of this study is that performance could be related to different Flanker tasks in relation to the most severely affected domain of apathy: cognitive apathy

may mainly affect the L-FT, emotional–affective apathy could influence the F-FT, and the auto-activation apathy the H-FT. However, this hypothesis was only partially and shily supported by data. Cognitive apathy showed a poor influence on the subjects' responses. Conversely, emotional–affective apathy revealed a transversal effect on about all types of tasks: results show that the more severe is the emotional affective apathy the more is the number of missing responses.

A specific effect was found only for "auto-activation" apathy that was significantly correlated with GIP in congruent trials of H-FT, and with number of H-FT congruent and incongruent missing trials. This result partially support the hypothesis that the subdomain of apathy could be related to the specific type of Flanker task since, in this case, auto-activation apathy was associated to H-FT, with worse responses for patients showing this specific apathy subtype. However, these findings suggest that it is possible that apathy symptoms may impair performance on any task, as a result of general lack of motivation showed by these patients.

However, about the H-FT, it is important to underline that, since participants performed sequentially two sessions of each task in which the stimulus-response mapping was inverted (see paragraph 3.2.3), in the session where subjects were asked to press key "P" when the target showed the right-pointing direction and "Q" for the left-pointing direction, there was a spatial compatibility effect, that may have contributed to the better performance obtained, in terms of GIP and RTs, by the three Groups in this Task.

The two groups of patients resulted well matched for all the analyzed demographical and clinical parameters. Only TMT_A resulted significantly different among the two groups, but it was found related to cognitive apathy, a parameter which poorly affects subjects' performances. Thus, it can be deduced that attention, one of the cognitive processes explored by TMT_A which, in turn, was found related to cognitive apathy, could have a poor influence on subjects' responses.

Finally, given the higher number of missing responses showed by ApABI patients in all the three tasks, mainly in incongruent trials, the results may suggest a potential link between apathy following severe ABI and conflict monitoring processes, even though further investigations are needed.

This study was conducted under some constraints and the major limitation is the small sample size, given the difficulty of enrolling ABI patients both with diagnosis of apathy and who did not show sensory-motor deficits (e.g. hemi-spatial neglect or visual disorders), that would make it impossible to execute the tasks. The small sample size limits the generalizability of findings to larger patient populations and the ability to determine the substantial role of apathy on conflict monitoring. For this reason, the results can only be interpreted with caution.

In spite of these limitations, the strength point of this study is the implementation of the H-FT, realized with the hypothesis that the "communicative gesture" of pointing could have activated the thoughts necessary to spontaneously initiate the motor program, usually compromised in patients with auto-activation deficit.

What should be done in the future is to provide further studies with larger sample size, in order to test the generalizability of the present results. It could be important to supply more evidences for the cortical processing of conflict control, by means of event-related potentials recordings. More specifically, it could be interesting to address the neural correlates of cognitive control on affective conflicts, to reveal the possible interplay between conflict control and facial expression perception in ABI patients with diagnosis of apathy. For instance, some studies on emotional F-FT (Horstmann et al., 2006) revealed that when the target is friendly and distractors are angry, the flankers attract more attention away from the target producing conflict, while when the target is negative (angry face) and flankers are positive (happy faces) attention is attracted to the target and away from the

flankers, reducing possible conflicts. This result indicates that the negative target stimulus narrows the focus of attention, whereas positive stimuli may broaden it.

In conclusion, apathetic manifestations are commonly reported in the ABI population and have been considered to be one of the greatest barriers to reintegration into the community, affecting motivation to engage in rehabilitation and have been also associated with a wide range of negative consequences for the patients and their caregivers (López-Dóriga Bonnardeaux and Andrino Díaz, 2016). This study represents a first step in understanding the apathetic symptoms which impact significantly on patient QoL, suggesting that a more routine assessment of apathy is required, mainly to discriminate it from depression.

Further studies are also necessary to better identify the underlying mechanisms of apathy in order to develop targeted and effective rehabilitation programs, decrease the level of disability and improve the social participation.

Chapter 4

Mood disorders after stroke

"Depression is when you don't really care about anything.
Anxiety is when you care too much about everything.
Having both is just like hell."

(Anonymous author)

4.1 Post-stroke mood disorders: depression, anxiety, post-traumatic stress disorders and pseudobulbar affect

Acute stroke is one of the important types of cerebrovascular diseases threatening the life and health, including hemorrhagic stroke and ischemic stroke (Wu and Zhang, 2017). It is a leading cause of movement disability in the US and Europe (Rosamond et al., 2007) and, by 2030, it has been estimated that 70 million stroke survivors could be around the world (Feigin et al, 2010).

Stroke consequences can include physical or cognitive deficits (i.e. memory, concentration), and language disorder: indeed, up to 70% of stroke patients experience cognitive deficits (Lesniak et al., 2008; Nys et al., 2007) and about one-third of them develop aphasia (Engelter et al., 2006; Laska et al., 2001).

Concerning mobility recovery, a 2008 study (Paolucci et al.) showed that about 50% of patients with stroke leave the rehabilitation hospital on a wheelchair, <15% are able to walk indoor without aids, <10% are able to walk outdoor, and <5% are able to climb stairs. Five years after stroke, approximately a third of those affected are moderately to severely disabled (Wilkinson et al., 1997).

Post-stroke rehabilitation demand will increase in the near future, leading to stronger pressure on health care budgets. For example, in the US, the estimated direct and indirect cost of stroke in 2010 was $73.7 billion, and the mean lifetime cost of ischemic stroke was estimated at $140.048 (Lloyd-Jones et al., 2010).

Given the several and complex consequences due to the stroke, it is understandable that emotional difficulties and psychiatric disorders are common in this specific clinical population, and can have an impact on rehabilitation outcome.

Different authors (Lindén et al., 2007; Merriman et al., 2007; Gupta e tal., 2008) agree that there is a significant correlation between stroke and *depressive disorders* and the two types most associated with stroke are major depression and minor depression, the latter of which has been defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 2000) criteria as a "depressed mood or loss of interest and at least 2 but fewer than 4 symptoms of major depression".

Prevalence rates for depression are around 31% (Hackett and Pickles, 2014), even though the same Authors (Hackett et al., 2005), on the basis of data collected from 51 studies on post-stroke depression (PSD), stated that it is likely to be an underestimation of the frequency with which PSD occurs. Errors in estimation may be attributed to under-reporting of unusual mood, difficulties in the assessment of depression in neurologically impaired individuals, and in the tool variability used to assess and define depression or "caseness" within the literature (Hackett et al. 2005). Furthermore, estimates of prevalence may be affected by the time from stroke onset until assessment. Patients who are evaluated during the subacute phase, may be in a period of transition during which they are attempting to adjust to the consequences of stroke, and depression, at this time, may simply be a reflection of the difficulties associated with this transition. Indeed, the highest rates of depression have been reported in the first month following stroke (Aben et al. 2006, 2003; Bhogal et al. 2004; Bour et al. 2010; Morrison et al. 2005), whilst Bour et al. (2010)

revealed a decrease in incident cases of depression over the course of the first year following the stroke event. Paolucci et al. (2005) reported that of 1064 patients included in the DESTRO study, 36% developed depression: in this study, dysthymia (mild depression) was the most common form of depression occurring in 80.7% of cases, whereas major depression was diagnosed in only 2.9%.

Prevalence of PSD should not be considered as static. While there may be a general trend toward improvement in depressive symptomatology over the first year following stroke (Ostir et al. 2011; Bour et al. 2010, 2011), PSD may be persistent for a significant proportion of individuals identified as depressed (Ayerbe et al. 2011; Berg et al. 2003; Farner et al. 2010; Ostir et al. 2011). Indeed, Farner et al. (2010) reported persistent depression in more than half (55%) of the individuals diagnosed as depressed during inpatient rehabilitation post stroke: significant predictors of persistent depression included lower levels of pre-stroke social activity, greater severity of stroke and lower levels of function at baseline. At the same time, other psychological aspects may be attributable to the development and sustainment of depression. Van Mierlo et al. (2015) showed that patients with specific personality traits and cognitions (e.g. with higher scores in the "neuroticism dimension" of the Eysenck Personality Questionnaire) are more susceptible to depression than those with more optimistic, extraverted and self-efficacious personality traits.

Depression has also been found to be comorbid with other symptoms of psychological distress, such as anxiety: in fact, White et al. (2014) reported that comorbid depression and anxiety at baseline was 69% and 34% at 12 month follow-up: although rates of depression remained consistent over the 12 month study period, anxiety decreased from 47% at baseline to 14% at the study's end.

Anxiety is a common neuropsychiatric complication of stroke with an estimated frequency between 20 and 25% (Campbell Burton et l., 2013) and, even though it is more common

than depression (Menlove et al., 2015), poststroke anxiety (PSA) has only recently gained attention whereas PSD has received most research attention (Wu et al., 2014).

As for depression, PSA is distressing for both patients and their caregivers, and negatively influence their QoL (Kim, 2017), since it leads to poorer adaptive functioning and relationships (Ferro, et al., 2009; West et al., 2010). Anxiety predicting factors and pathophysiology have been under-studied and are under-recognized, and its symptoms are not apparent and are therefore often neglected by clinicians (Kim, 2017). Furthermore, female gender and younger age than 65 years have been evaluated as the most common risk factors for PSA (Tang et al., 2013; Ayerbe et al., 2014).

Another psychological complication of stroke is the *PTSD*, an anxiety disorder initiated by exposure to a traumatic event and characterized by symptoms of re-experiencing, avoidance of reminders of the event, persistent negative mood and cognition, and physiological hyperarousal persisting for at least one month after the event (Edmonson et al., 2013). PTSD is known to occur after exposure to combat or other life threatening violence (e.g. sexual assault) (Polusny et al., 2011), but it can also develop as a result of life-threatening medical conditions as varied as Human Immunodeficiency Virus (Sherr et al., 2011), breast cancer (O'Connor et al., 2011), acute coronary syndromes (Bennett and Brooke, 1999; Edmondson et al., 2011, 2012) and stroke (Merriman et al., 2007; Bruggimann et al., 2006; Field et al., 2008; Sagen et al., 2009; Wang et al., 2011; Letamendia et al., 2012).

Observational evidence suggested that PTSD is related to increased risk of incident cardiovascular disease (Kubzansky et al., 2007; Boscarino, 2008) as well as, according to Edmondson and coll. (2011, 2012), PTSD triggered by cardiovascular events (specifically, acute coronary syndrome) is associated with a doubling of risk for recurrent cardiac events and mortality.

Nevertheless, few studies assessed PTSD due to stroke where its reported prevalence, among104 patients evaluated from 3 months to 4 years after stroke, ranges from 3–37% (Merriman et al., 2007; Bruggimann et al., 2006; Field et al., 2008; Sagen et al., 2009; Wang et al., 2011; Letamendia et al., 2012). In these studies, PTSD was associated with sociodemographic factors, such as female gender and poor education (Bruggimann et al., 2006; Letamendia et al., 2012), and with psychological factors including distress at the time of stroke (Letamendia et al., 2012), and more negative cognitive appraisals of the stroke (Bruggimann et al., 2006; Field et al., 2008).

A study conducted by Kronish and coll. (2012) found that 18% of 535 stroke or transient ischemic attack (TIA) survivors reported clinically significant PTSD symptoms, showing that they were nearly three times more likely than those without PTSD symptoms to report medication nonadherence. Similar results were reported by Edmondson and coll. (2013), who found that 1 in 4 stroke or TIA survivors developed significant PTSD symptoms due to the stroke or TIA.

Another emotional effect of stroke is the *pathological crying or laughing,* which has been given many different labels within the literature including emotional incontinence, emotional lability, pathological display of affect, pseudobulbar affect or emotionalism (Andersen et al. 1995a).

While there appears to be no consensus regarding the most appropriate label or diagnostic criteria for this condition, many reports refer to the definition provided by House and colleagues (1989) as “an increase in tearfulness with episodes of crying that were sudden or unheralded and not all under normal social control”. This definition focuses on pathological crying, but similar criteria were also applied to pathological laughing (House et al. 1989).

Pseudobulbar affect occurs primarily in patients with neurologic disorders such as stroke, trauma, and multiple sclerosis (Takeuchi et al., 2014), and patients may find themselves

crying uncontrollably at something that is only moderately sad, being unable to stop themselves for several minutes, or may laugh uncontrollably when angry or frustrated.

Patients who are the least affected may present with excessive and/or inappropriate facial grimacing. In either case, individuals experiencing post-stroke pseudobulbar affect may withdraw from participation in normal social roles due to distress and fear of social embarrassment (Andersen 1995).

Pathological laughing and/or crying is often misunderstood by patients and their families, it is under-recognized by the clinicians, and its prevalence is much higher than expected (work et al., 2011; Strowd et al., 2010). However, the reported frequency of pseudobulbar affect following stroke ranges from 11% (House et al. 1989) to 34% (Kim and Choi-Kwon, 2000), even though the criteria used to define emotionalism and the time elapsed since stroke onset were differed among these Authors; clearly, there is a need to develop a single set of criteria with which to diagnose post-stroke pseudobulbar affect.

Risk factors have not been well defined: pseudobulbar affect has been associated with younger age (Calvert et al., 1998), female gender (Kim and Choi-Kwon, 2000), cognitive and motor impairment (Andersen et al., 1995b; House et al. 1989, Kim and Choi-Kwon, 2000), ischemic stroke vs. haemorrhagic stroke (Kim and Choi-Kwon 2000), and history of depression and cortical infarcts (Tang et al. 2004).

A significant association has been reported between post-stroke emotionalism and PSD (Andersen et al., 1995; Calvert et al., 1998; House et al., 1989; Kim and Choi-Kwon, 2000; MacHale et al., 1998), though most individuals with post-stroke pseudobulbar affect do not have significant or diagnosable depression (Calvert et al. 1998; Kim and Choi-Kwon, 2000). Furthermore, both Eccles and coll. (1999) and Calvert et al. (1998) reported that pseudobulbar affect was associated with significantly greater emotional distress and other psychiatric disorders.

Finally, also *fears* are common in stroke patients, and up to 60% of them develop the fear of falling (Watanabe, 2005). Other commonly encountered fears include that of having another stroke; of not regaining functional abilities such as swallowing, continence, walking, and language; of not being able to return to own home, to start driving again or work (Lincoln et al., 2012), while the less common fears showed by stroke patients are those influenced by spatial neglect (e.g., the fear of "falling into an abyss") and those specific to individual premorbid function (e.g., "not being able to ice skate proficiently").

4.2 Treatment of post-stroke mood disorders

Mood disorders after stroke are common and disabling and can have an impact on rehabilitation outcome: depression, for instance, is associated with longer hospital stays, reduced participation in rehabilitation, increased physical impairment and handicap, as well as increased mortality (Ebrahim et al. 1987; House et al., 2001; Morris et al., 1993; Sinyor et al., 1986).

PSD may be treated by means of both phamacological and non-pharmacological interventions, and the drug therapy for depression is based on the notion that this clinical condition is associated with an imbalance and under-activity of the cerebral noradrenergic and serotonergic systems (Takeuchi et al., 2014). In a meta-analysis of 16 studies, Chen and coll. (2006) reported a significant reduction in depressive symptomatology on all scales used to assess outcome, identifying a relationship between duration and benefit of pharmacological intervention: treatment duration of 3 weeks onward revealed significant positive effects. Likewise, Hackett and coll. (2008), by examining the use of pharmacological interventions for the PSD treatment, concluded that use of pharmacotherapy was associated with a small, but significant, positive treatment effect.

However, this should be considered in light of side effects associated with the use of antidepressant medications. Indeed, some studies examined the potential risks associated

with the use of antidepressants in older individuals (Coupland et al. 2011; Wu et al. 2011), which demonstrated increased risk for some adverse outcomes as stroke/TIA. In particular, Coupland and coll. (2011) identified a large cohort of individuals with diagnosis of depression with an age higher than 65, where the use of antidepressant drugs was associated with significantly increased risk of adverse outcomes including all-cause mortality, attempted suicide/self-harm, falls, and fractures. The pattern of association with adverse outcomes varied with the class of drug examined: more specifically, the use of Selective Serotonin Reuptake Inhibitors (SSRIs) was associated with the greatest risk for falls and hyponatraemia.

In the retrospective study conducted by Ried and colleagues (2011), the treatment with SSRI antidepressant prior to stroke, was only associated with an increased risk for mortality following stroke, even though the SSRI treatment for depression both before and after the stroke, was found to be protective for mortality when compared to no post-stroke treatment.

Psychostimulants (such as methylphenidate), used for treating attention-deficit disorders, have been revealed to be an effective treatment for PSD. More specifically, methylphenidate has its effects in the cortical and subcortical areas of the brain and, thus, is thought to heighten mood by affecting several neurotransmitter systems, in particular the noradrenergic system. In addition, it blocks the reuptake of serotonin and norepinephrine and has dopaminergic activity and, therefore, it is thought that methylphenidate may affect PSD by correcting the depletion of biogenic amines caused by stroke, and to relieve apathy (Johnson et al. 1992).

As for *non-pharmacologic treatments* of PSD, there is some evidence that psychological interventions, such as motivational interviewing and problem solving, may prevent depression after stroke (Hackett et al., 2008).

The efficacy of Cognitive-Behavioral Therapy (CBT), a psychological approach assessing dysfunctional emotions and thoughts and maladaptive behaviours, and aiming to mitigate psychological disorders (Beck, 1967), is supported by studies on patients with diagnosis of ABI (Stalder-Lüthy et al., 2013; Waldron et al., 2012) and other neurological conditions, such as multiple sclerosis (Hind et al., 2014) and Parkinson's disease (Armento et al., 2012; Dobkin et al., 2011). Using CBT to treat depression after stroke was first described in a single-case study (Hatcher et al., 1985) as part of a successful multidisciplinary approach.

However, Lincoln and Flannaghan (2003) compared, in post-stroke patients with depression, the CBT intervention (provided up to 10 sessions) with an attention placebo and standard care, and they found no significant difference between the groups, in terms of improvements in depression scores. Different explanations have been provided to describe this result, including the low number of CBT sessions and the fact that those who benefited least had poorer communication skills, suggesting that treatment of PSD requires a modified and tailored approach, able to circumvent the communication disabilities often shown by stroke patients (Lincoln and Flannaghan, 2003). Conversely, Chang and coll. (2011) compared a counseling intervention similar to CBT with an usual care, and found that depressive symptoms improved in the patients group received the CBT intervention.

While there is some evidence for CBT efficacy in treating PSD, very little is known about its effects on PSA (Kneebone and Jeffries, 2013). In the same way, much is still unknown regarding the effect of relaxation therapy (a behavioural technique which helps to break the cycle of stress response favouring physiological and psychological relaxation; Anand, 2006) on post-stroke mood disorders and, more specifically on PSA, and further studies are warranted.

Finally, there are few studies also regarding effective interventions on post-stroke pseudobulbar affect, and the most common treatment consists of antidepressant drugs, in

particular SSRIs (Takeuchi et al., 2014), which are associated with reduction in the frequency and severity of pathological crying episodes (House et al., 2004). However, as noted by House and coll. (2004), study results about the SSRIs efficacy on post-stroke emotionalism, should be interpreted with caution, since most studies were quite small and used different methods to define and assess the pseudobulbar affect, and to determine frequency and severity of episodes or outbursts. Thus, further investigations are required to better establish the efficacy of antidepressant drugs on pathological crying or laughing.

Chapter 5

A visual version of the Hospital Anxiety and Depression Scale: a preliminary validation study in Italian population

1. Introduction

As already widely discussed in the previous chapter, it is known that depression is common among stroke patients and compromises their functional recovery, reducing QoL and motivation for rehabilitation (Zahi et al., 2016). However, even though the "secondary depression" is the most prevalent psychiatric disorder in stroke patients, there is growing evidence that depression may increase the risk of stroke considered, therefore, as consequence of depression (primary depression) (Barlinn et al., 2014). In fact, in the early 1990s, evidence appeared to indicate that medically healthy depressed patients were at significantly increased risk of developing heart attacks and strokes later in life (Glassman, 2007). Thus, depression and stroke are intimately associated and present a complex relationship, and the Guidelines regarding the management of stroke patients strongly recommend to carry out a screening for depression and anxiety in this clinical population (Jauch et al., 2013, Miller et al., 2010; Duncan et al., 2005; Gooskens et al., 2009). There are many instruments to evaluate Post Stroke Depression (PSD), but the optimal screening tool is still unclear. Meader and coll. (2014) conducted a meta-analysis to determine which screening tools were most accurate for detecting PSD, showing that the 20-item Center of Epidemiological Studies-Depression Scale (CES-D) (sensitivity: 0.75; 95% CI, 0.60–0.85;

specificity: 0.88; 95% CI, 0.71–0.95), the 21-item Hamilton Depression Rating Scale (HDRS) (sensitivity: 0.84; 95% CI, 0.75–0.90; specificity: 0.83; 95% CI, 0.72–0.90), and the 9-item Patient Health Questionnaire (PHQ-9) (sensitivity: 0.86; 95% CI, 0.70–0.94; specificity: 0.79; 95% CI, 0.60– 0.90) appeared to be the most effective tools. Although CES-D and HDRS had high sensitivity, they may not be feasible in clinical practice, and PHQ-9 may be more pragmatic.

An understanding of the pathophysiology of PSD may aid in its management: PSD resulting from biological causes could potentially respond better to pharmacological therapy, whereas PSD resulting from psychosocial causes could possibly respond more favorably to psychotherapy and social support interventions (Towfighi et al., 2017). Hackett and coll. (2008) observed that post-stroke depressed patients may benefit from antidepressant treatment even though it is often associated with important side effects, while according to other studies (Kim et al., 2014) the incidence of PSD may be reduced by means of taking statins. About the psychological intervention, there is a lack of well-designed trials of psychosocial approaches for the PSD treatment, with no evidence of benefit of psychotherapy (e g., cognitive behavioral therapy, motivational interviewing, etc.) (Hackett et al, 2008). To suitably manage depression in these patients, integrative approach including antidepressant drugs, treatment of the physical disorder, and modification of coping styles should be warranted (Kang et al., 2015). Nevertheless, depression remains still unrecognized, undiagnosed and insufficiently treated (El Husseini et al., 2012).

Nearly a quarter of survivors from a stroke suffer from anxiety disorders (Mavvadat et al., 2017) as well. These are more stable and persistent than PSD (Bergerson et al., 2010) and can further negatively impact the prognosis of depression (Aström, 1996), as well as the QoL (Ahlsio 1984). Moreover, the prevalence of anxiety after stroke ranges from 20% to 25% (Campbell Burton, 2013), and it represents a common problem with PSD after the

stroke event (Ayerbe 2013; Langhorne 2000). Anxiety is more common, after stroke, among younger or female people, those unable to work and with lower income backgrounds (Ayerbe 2013; Broomfield 2015; Menlove 2015). Different types of anxiety disorders are diagnosticable, such as general anxiety disorder, panic disorder, social phobia, obsessive-compulsive disorder, and PTSD, which may be treated with both pharmacological and psychological interventions (Knapp, 2017).

Different tools are used to evaluate "mood disorders" in post-stroke patients: the 30-item Geriatric Depression Scale (GDS-30, Yesavage et al., 1983) and the General Health Questionnaire in its 28 item version (GHQ-28, Caplan, 1994) were revealed to be more satisfactory screening instruments both for PSD and anxiety disorders (Johnson et al., 1995). In a study by Vicentini and coll. (2016), the BDI (Beck et al., 1961) and Beck Anxiety Inventory (Beck et al., 1988) were administered to subacute ischemic stroke patients in order to measure depressive and anxiety symptom severity respectively, while Schöttke and Giabbiconi (2015) investigated post-stroke affective disorders by means of the Structured Clinical Interview (First et al., 1996) relying on the Diagnostic and Statistical Manual of Mental Disorders IV.

However, the Hospital Anxiety and Depression Scale (HADS) is one of the most used tool to assess anxiety and depression in clinical setting. It was developed by Zigmond and Snaith (1983) to assess the presence of mood disorders among patients in non-psychiatric hospital clinics. The questionnaire is composed by two seven-item-subscales, which measure anxiety and depression, respectively; the two subscales are motivated by the distinction that the authors accurately define between the two constructs of depression and anxiety. Each item identifies potential recent changes in person's mood, comparing the feeling intensity in the last week with the intensity usually felt by the individual before the illness-onset. The main problem in using the HADS with post-stroke patients is that this scale asks for spared abilities in language, in particular in the reading and comprehension

of the items. For this, depression or anxiety in patients suffering from aphasia may be not identified or under-estimated. This represents a relevant limitation for rehabilitation, as just the presence of aphasia may trigger or increase the patients' depressive symptoms (Aben et al., 2002). Van Dijk and colleagues (2015) identified six tools to mainly evaluate depression in stroke patients with aphasia: The Aphasic Depression Rating Scale (ADRS; Benaim et al., 2004), the Clinical Global Impression-Scale (CGI-S; Guy, 1976), the Stroke Aphasic Depression Questionnaire in four versions [SADQ (21 item); the 21 item Hospital version (SADQ-H21); the 10 item SADQ (SADQ-10) and the 10 item Hospital version (SADQ-H10)] (Sutcliffe and Lincoln, 1998; Lincoln et al., 2000) , the Signs of Depression Scale (SODS, Hammond et al., 2000), The Visual Analogue Mood Scale (three versions) (VAMS; Folstein et al., 1973; Stern et al., 1997; Kontou et al., 2012) and the Visual Analogue Self Esteem Scale (VASES; Brumfitt and Sheeran, 1999) (see Table 5.1), all of them quick to administer in maximum five minutes. However, none of these tools showed satisfactory reliability and validity even though SADQ-10 (Sutcliffe and Lincoln, 1998), SADQ-H10 (Lincoln et al, 2000) and SODS (Hammond et al., 2000) revealed acceptable feasibility (van Dijk et al., 2015).

Full Name	**Abbreviation**
Aphasic Depression Rating Scale	ADRS
Clinical Global Impression-Scale	CGI-S
Stroke Aphasic Depression Questionnaire (21 items)	SADQ
Stroke Aphasic Depression Questionnaire-Hospital version (21 items)	SADQ-H21
Stroke Aphasic Depression Questionnaire (10 items)	SADQ-10
Stroke Aphasic Depression Questionnaire-Hospital version (10 items)	SADQ-H10
Signs of Depression Scale	SODS
Visual Analogue Mood Scale (8 items)	VAMS 8-items
Visual Analogue Mood Scale (single item)	VAMS single item
Visual Analogue Mood Scale-Revised	VAMS-R
Visual Analogue Self-Esteem Scale	VASES

Table 5.1. Tools assessing depression in stroke aphasic patients (van Dijk et al., 2015).

Since a gold standard evaluation of mood disorders among this clinical population has to be identified yet, the aim of this study was to develop a visual version of the HADS, which is based on pictures easily understandable allowing the detection of the possible presence of depression and anxiety symptoms in patients with aphasia. This study is the first step of the validation process of the visual version of the HADS: in order to study its reliability and equivalence with the original Scale (i.e., the written form; Zigmond and Snaith, 1983), we administered the Written and Visual forms to a wide sample of healthy Italian subjects. More specifically, our aim was to verify that each item of the HADS was well depicted by each picture of the HADS visual form.

5.2 Methods

5.2.1. Participants

Two hundred healthy subjects (61 males, age: 42.11 ± (SD) 12.33; 139 females, age: 38.37 ± 11.63) without any neurological or psychiatric diseases, voluntary participated to the study. Educational years ranged from 8 to 17 (only one person had 5 years of education) without significant differences between males and females (middle school: $\chi^2_{(1)} = 0.36$, $p = 0.55$; high school: $\chi^2_{(1)} = 0.29$, $p = 0.59$; $\chi^2_{(1)} = 0.35$, $p = 0.55$).

Post-hoc pairwise t-tests with Bonferroni correction, showed that participants with Master degree (age: 38.81 ± 9.87) were younger both than people with high school ($p = 0.026$, age: 41.34 ± 12.78) and lower secondary school education ($p < .001$, age: 55.71 ± 11.44). A statistically significant difference was also found between the latter two educational levels (high school vs. a lower secondary school; $p = < .001$).

The study was approved by the local Ethical Committee of the Neurorehabilitation Hospital, Fondazione Santa Lucia, in Rome.

5.2.2. Materials

The HADS (Zigmond and Snaith, 1983) is a fourteen item questionnaire, with seven items assessing anxiety (e.g. *I can feel relaxed*) and seven assessing depression (e.g. *I feel as if I am slowed down*). Each item is rated on a scale from 0 (e.g. *as much as I always do*) to 3 (e.g. *not at all*), giving maximum scores of 21 for each subscale (i.e. depression subscale, HADS-D; anxiety subscale, HADS-A). The questionnaire rates symptoms referring to the last week (See Appendix 2).

In order to realize the visual form of the HADS (Zigmond and Snaith, 1983), an expert cartoonist draw a vignette for each item of the Scale. More specifically, two vignettes were created for each item to have both a man and woman as main character (see Figure 5.1 *a and b*): the female or male stimulus was chosen based on the participant's gender.

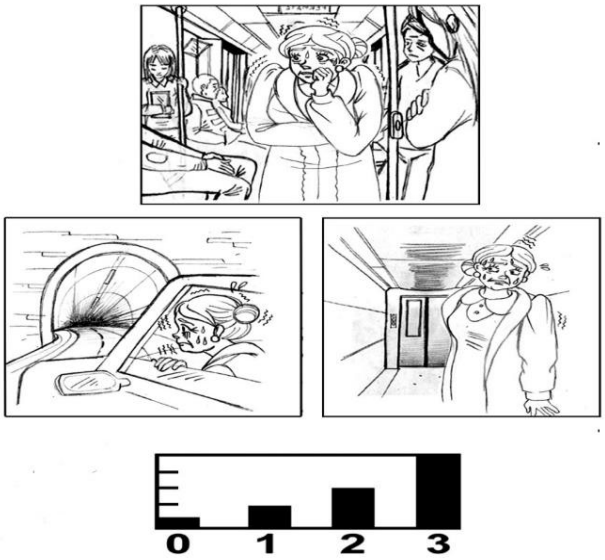

Figure 5.1a depicts the HADS item: *I get sudden feelings of panic*, in its visual version with a wowan as main character. In this case, scores indicate as following: 0 =*Not at all*, 1=*Not very often*, 2= *Quite often*, 3= *Very often*.

Figure 5.1b shows the HADS item: *I feel cheerful*, in its visual version with a man as main character. In this case, scores indicate as following: 0=*Most of the time*, 1=*Sometimes*, 2=*Not often*, 3= *Not at all*.

5.2.3. Procedure

Both the visual and written version of HADS were uploaded in an on-line survey (Survey Monkey Inc., Palo Alto, California USA, www.surveymonkey.com), whose link was sent by e-mail to 360 subjects, selected from a mailing list of people who had previously expressed their willingness to volunteer for research studies. The 55% of them accepted to participate to the study, resulting in a final total sample of 200 healthy subjects.

Socio-demographic characteristics of the participants (such as gender, age, education) were collected at the beginning of the survey, and each of them was assigned a numerical code to maintain privacy and confidentiality.

In the first phase, the HADS visual form (i.e. vignettes) was presented, and each participant was asked to refer how many times he or she felt the mood represented in the picture, by indicating a value from 0 to 3 (e.g. 0=never; 1=sometimes; 2=often; 3=always).

In the second phase, the HADS written form (the original version by Zigmond and Snaith) was provided and subjects had to answer to the fourteen questions of the Scale, according to the same range of values of the previous phase (i.e., from 0 to 3).

Finally, in the last phase both visual and written form of the HADS were presented, and participants were asked to associate each question with the right picture, in order to assess the equivalence between the two forms of the Scale (see Figure 5.2).

There was no time limit to complete the survey, and participants were aware that there were no right or wrong answers, nor they would have received any feedback.

At the end of the survey, people have been thanked for their cooperation.

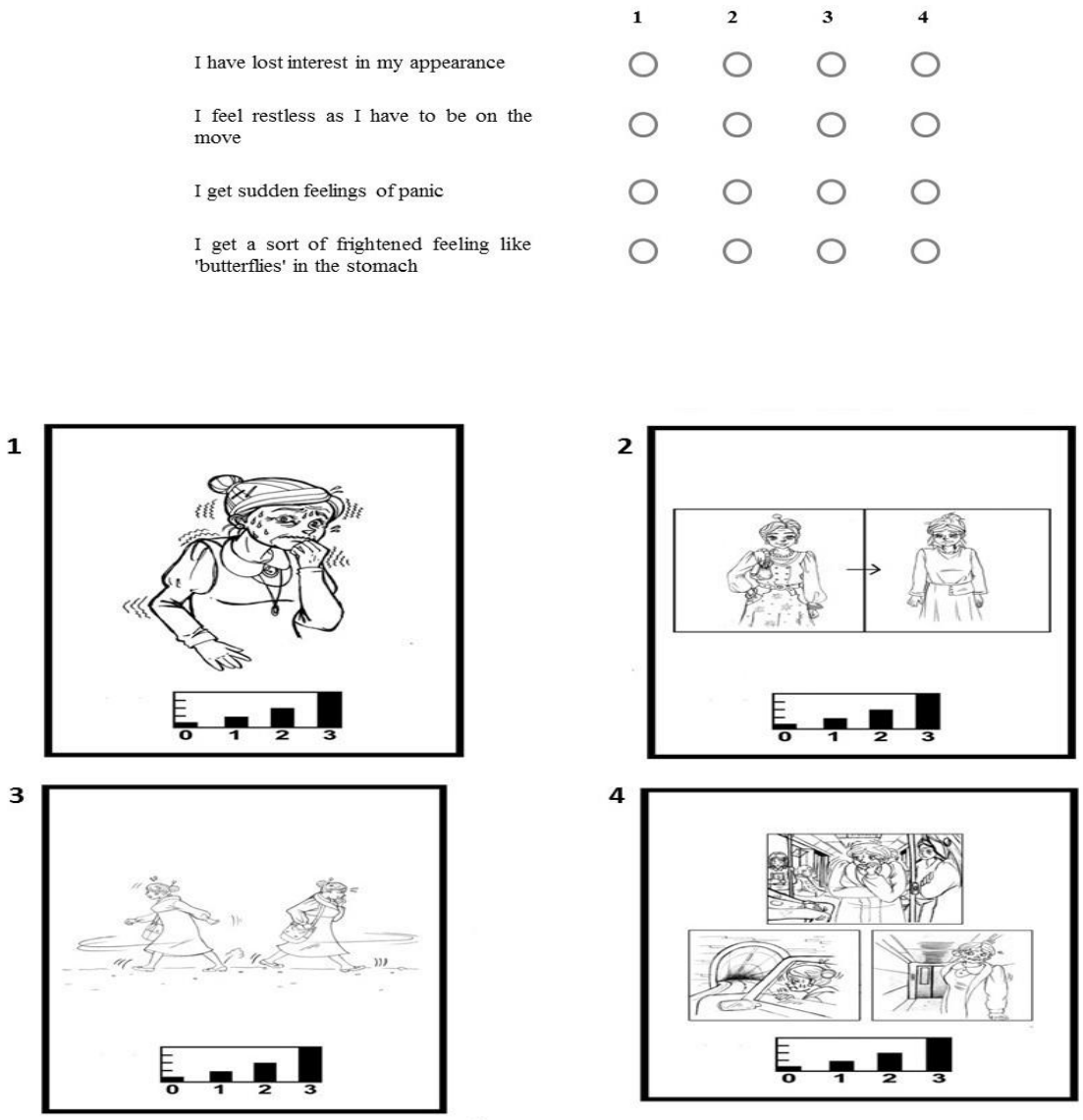

Figure 5.2 shows the third phase of the on-line survey: "*Please, choose the right picture for each sentence, by writing the corresponding number*".

5.2.4. Statistical analyses

In both HADS versions, items n° 2, 4, 6, 7, 12 and 14 have a positively valence, but with a reversed response and different scores (e.g. 0= Definitely, 1= Usually, 2= Not often, 3=Not at all) than the items with negatively valence (e.g. 0=Not at all, 1=Sometimes, 2= Very often, 3=Nearly all the time).

Through the Principal Component Analysis (PCA) (Horn, 1965), considered one of the best methodology for identifying the number of components of a dataset (Zwick & Velicer, 1986), we determined the number of components to be extracted, and proceeded with two distinct PCAs (one for the written and one for the visual form), with the purpose to observe similarities and differences in the structure of the two versions.

We obtained two different categories of components: i) "positive" referred to the six items with a positively valence, ii) "negative" related to those with a negatively one (eight item). Since the HADS-A and HADS-D subscales are highly correlated (from .40 to .74, Bjelland et al., 2002), we used the Oblimin rotation method in order to allow correlations among components. PCA returns a numeric matrix of loadings, interpreted as how much a question is representative of the component in a range between 1 and -1. In this way, we assessed the most important questions for each component, the items to be subtracted (i.e. negative loadings), added (i.e. positive loadings), or ignored (i.e. loadings between 0.3 and -0.3). The components usually are named after the most representative questions (i.e. higher loadings). This analysis does not guarantee that components will mirror the original HADS subscales, but it is precious to understand if the written and visual forms are similar.

Subsequently, we computed the scores for each component of both the written and visual forms. For components with the same number of items, the scores were obtained by adding all questions whose loading ≥ 0.3, and subtracting all questions whose loading $\leq$-0.3; for all components, Cronbach's alpha was computed. If the number of questions for each

component was different, scores with loadings less than -0.3 were multiplied by -1; subsequently, these values were averaged with the scores of questions with loadings greater than 0.3

We performed a Bayesian ANOVA to observe possible differences between the scores of the obtained components in the two HADS forms, and verify both the alternative hypothesis and the null hypothesis. This statistical approach computes Bayes Factors (BF) for each main effect or interaction of the ANOVA, with a BF estimated against the null hypothesis. A BF is the ratio of the likelihood probability of two competing hypotheses (in this case the null and the alternative hypothesis). The standard convention for BFs is: if the BF is greater than 3 the alternative hypothesis should be accepted, if it is less than 0.3 the null hypothesis should be accepted. Post-hoc tests were carried out by means of Bayesian t-tests, taking into account a null Interval delimited by the double of the standard deviation (2SD) of data. We contrasted two hypotheses: the null hypothesis was that the differences between two subsets of data were within 2SD, the alternative hypothesis was that these differences were outside the 2SD range.

Furthermore, we executed the Confirmatory Factory Analyses (CFA) in order to verify if the original division proposed by Zigmond and Snaith (1983) in the HADS-D and HADS-A subscales was confirmed and suited both the written and the visual form. Specifically, by using the two designs from the PCA and from the original "Depression-Anxiety" division, we employed two CFA models and compared the resulting models by means of Log-Likelihood Ratio Test.

Finally, we computed an additional Bayesian ANOVA to detect possible differences between the written and visual HADS form.

Analyses were carried out using: i) the R software for statistical analysis, ii) the package psych for the Cronbach's alpha to evaluate the internal consistency of the scales, parallel analysis and PCA, iii) the package lavaan for the structural equation models of the CFA,

iv) and the package BayesFactor for Bayesian ANOVAs and Bayesian t-tests. We used the Jeffreys' scale to assess the evidence (Jeffreys, 1961). In particular, a BF10 > 3 meant that there was an effect, and thus that the alternative hypothesis was true, whereas the null hypothesis was true when a BF10 < 0.3. When we had extreme BF10, we reported BF10 < 0.001 or BF10 > 100.

5.3 Results

5.3.1. Principal Component Analysis (PCA)

The parallel analyses of the two HADS forms suggested the presence of two components (i.e. positive and negative), revealing a symmetric structure (see Table 5.2), with positively valence items (2, 4, 6, 7, 12, 14) and negatively valence ones (1, 3, 5, 8, 9, 10, 11, 13).

Both the positive and negative components showed a good level of internal consistency in the written form (Cronbach's α 0.87 and 0.80 respectively), according to the standard cut-off values (Good: $\alpha \geq 0.8$, Acceptable: $0.8 > \alpha \geq 0.7$, Questionable: $0.7 > \alpha \geq 0.6$, Kline, 2000). In the visual version the negative component reached an adequate Cronbach's α (0.73), while the positive component was 0.67. The written form reached an overall good level of reliability (0.83), while the Cronbach's α of the visual version was 0.62.

N°	Questions	Written form		Visual form	
		PC1	PC2	PC1	PC2
1	*I feel tense or 'wound up'.*		0.637		0.544
2	*I still enjoy the things I used to enjoy.*	0.787		0.645	0.645
3	*I get a sort of frightened feeling as if something awful is about to happen.*		0.598		0.680
4	*I can laugh and see the funny side of*	0.830		0.440	

	things.				
5	*Worrying thoughts go through my mind.*		0.593		0.450
6	*I feel cheerful*	0.834		0.617	
7	*I can sit at ease and feel relaxed.*	0.791		0.628	
8	*I feel as if I am slowed down.*		0.610		0.686
9	*I get a sort of frightened feeling like 'butterflies' in the stomach.*		0.789		0.702
10	*I have lost interest in my appearance.*		0.432		0.548
11	*I feel restless as I have to be on the move.*		0.705		0.519
12	*I look forward with enjoyment to things.*	0.773		0.665	
13	*I get sudden feelings of panic.*		0.726		0.552
14	*I can enjoy a good book or radio or TV program.*	0.638		0.663	
SS loadings		3.823	3.385	2.914	2.373
Proportion Var		0.273	0.242	0.208	0.169
Cumulative Var		0.273	0.515	0.208	0.378

Table 5.2. PCA loadings for the written and visual HADS forms. Loadings with absolute value lower than 0.3 have been removed. PC1= Positive Principal Component; PC2= Negative Principal Component. SS= Sum of squares. Var= variance

5.*3.2. Analysis of Positive and Negative components*

In order to compute the participants' scores in positive and negative components of the visual and written HADS forms, we considered the mean scores of the answers provided by subjects (see the paragraph 5.2.4). The written form scores were: in positive component 0.687 ± 0.262, and in negative 1.259 ± 0.296, whereas for the visual form were: positive 0.545 ± 0.224, negative 1.330 ± 0.261 (see Figure 5.3).

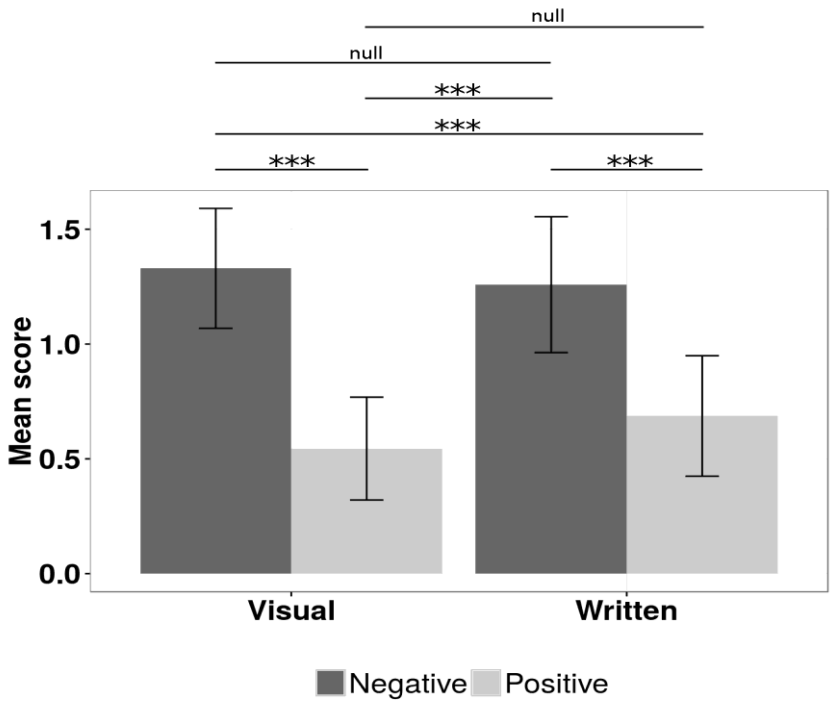

Figure 5.3. Mean and standard deviation of scores of the visual and written forms, computed on the Negative and Positive components. *** = BF ≥ 3; null = BF ≤ 0.3.

Bayesian analysis was computed by taking into account the fixed factors Form (Visual and Written), Component (Positive and Negative) and their interaction. As random factor we used the Subject's ID. Bayesian analysis showed that there was no statistically significant difference between the two HADS forms (BF = 0.156), while a significant difference was found between the Positive and the Negative components in both HADS versions (BF > 100). The interaction between Form and Component reached a BF greater than 100. Bayesian t-tests showed that the scores from the Written Positive and the Visual Positive scales were equal (BF = 0.003). Similar results were obtained in the Written Negative and Visual Negative scales (BF < 0.001).

CFA fitted the original division of the two subscales (i.e. HADS-A and HADS-D) (Zigmond and Snaith, 1983), and the "Positive-Negative" structure resulting from the

PCA, in both the written and visual HADS forms (see Figure 5.4), even though the fitting of the Models was not adequate [Root Mean Square Error of Aproximation (RMSEA) for the visual form of the "Depression-Anxiety" model: 0.11; RMSEA for the written form of the "Depression-Anxiety" model: 0.132; RMSEA for the visual form of the "Positive-Negative" model: 0.072; RMSEA for the written form of the "Positive-Negative" model: 0.08]: this may be related to the fact that our sample was consisted of healthy participants. The comparison, in the two HADS versions, between the structure emerged from the PCA and the original "Depression-Anxiety" model (Zigmond and Snaith, 1983) was not statistically significant different (LR $\chi 2$ = -169.29, p = 1; LR $\chi 2$ = -107.12, p = 1, respectively), showing that the two Models are similar (Figure 5.4).

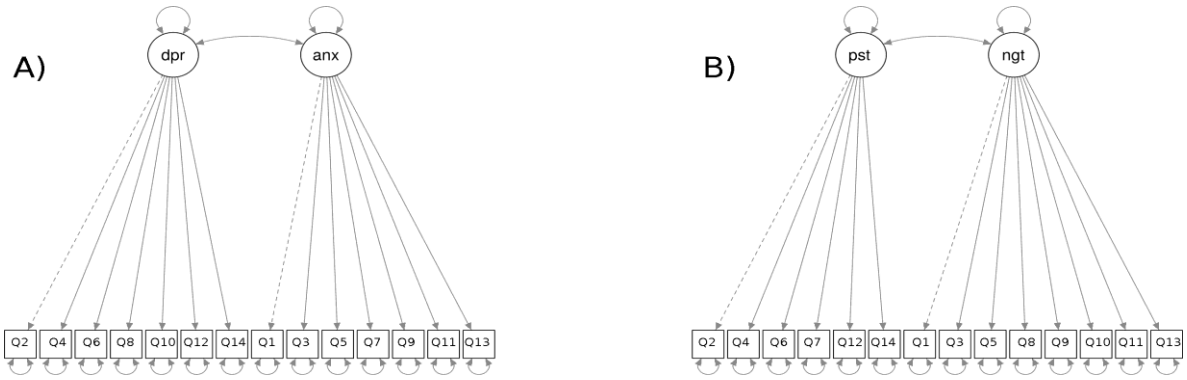

Figure 5.4. Models for CFAs. A) Model for the original "Depression-Anxiety" division. B) Model for the "Positive-Negative" division. Dpr = depression; anx = Anxiety; pst = Positive; ngt = Negative.

5.3.3. Analysis of Depression and Anxiety subscales

The scores of the HADS-A and HADS-D subscales were calculated by averaging the scores obtained from each question (written form: Depression 0.894 ± 0.245, Anxiety 1.051 ± 0.266; visual form: Depression 0.741 ± 0.223, Anxiety 1.133 ± 0.208, see Figure 5.5). For the Bayesian ANOVA, we used the Form (Visual, Written), the Mood

(Depression, Anxiety) and their interaction as fixed factor, and the Subject as Random Factor. The BF for the interaction was greater than 100. Direct comparisons through Bayesian t-tests showed that the Anxiety scales of the visual and the written forms were equivalent (BF < 0.001), while the comparison between the Depression scales of the two HADS versions were different (BF = 3.315). Moreover, within the visual form, a statistically significant difference between the HADS-A and HADS-D scubscales was found (BF > 100), while in the original written form (Zigmond and Snaith, 1983) this difference did not reach the decision boundaries (BF = 1.836).

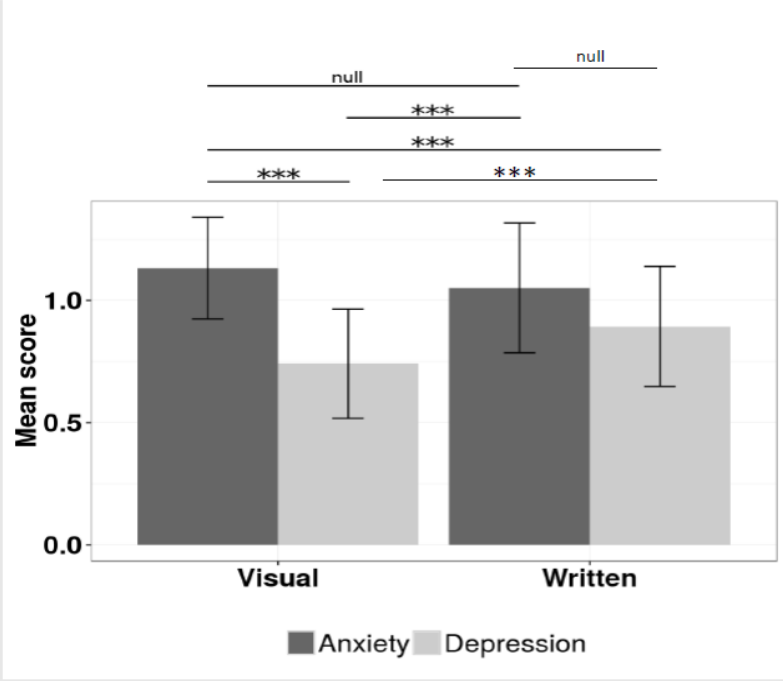

Figure 5.5. Mean and standard deviation of the scores of the Visual and Written form, computed on the Anxiety and Depression factors. *** = BF ≥ 3; null = BF ≤ 0.3

In both versions, the anxiety items showed a significant correlation with the HADS-A subscale (range 0.29 – 0.76 for the written form, 0.33 – 0.64; visual form, all ps < .01). Similarly, all the depression items correlated with the HADS-D subscale (range 0.54 – 0.74 for the written form, 0.30 – 0.70; visual form, all ps < .01). Likewise, all items showed a

significant correlation with the Full Scale (range 0.40 – 0.70 for the written form, 0.35 – 0.60 ; visual form, all ps < .01) (see Table 5.3 for the full list of correlations).

N°	HADS subscales	Questions	Written form			Visual form		
			Depression	Anxiety	Full Scale	Depression	Anxiety	Full Scale
1	*A*	*I feel tense or 'wound up'.*	0.74***	0.38***	0.65***	0.62***	0.23ns	0.52***
2	*D*	*I still enjoy the things I used to enjoy.*	0.37***	0.76***	0.63***	-0.05ns	0.59***	0.35***
3	*A*	*I get a sort of frightened feeling as if something awful is about to happen.*	0.62***	0.16ns	0.46***	0.67***	0.16ns	0.51***
4	*D*	*I can laugh and see the funny side of things.*	0.26**	0.75***	0.57***	0.02ns	0.45***	0.28**
5	*A*	*Worrying thoughts go through my mind.*	0.74***	0.43***	0.68***	0.50***	0.04ns	0.33***
6	*D*	*I feel cheerful.*	0.34***	0.75***	0.62***	0.17ns	0.64***	0.51***
7	*A*	*I can sit at ease and feel relaxed.*	0.54***	0.70***	0.70***	0.30**	0.38***	0.42***
8	*D*	*I feel as if I am slowed down.*	0.40***	0.29**	0.40***	0.49***	0.48***	0.60***
9	*A*	*I get a sort of frightened feeling like 'butterflies' in the stomach.*	0.68***	0.19ns	0.51***	0.70***	0.09ns	0.47***
10	*D*	*I have lost interest in my appearance.*	0.33***	0.41***	0.42***	0.33***	0.33***	0.41***
11	*A*	*I feel restless as I have to be on the move.*	0.69***	0.34***	0.60***	0.51***	0.15ns	0.40***
12	*D*	*I look forward with enjoyment to things.*	0.21ns	0.72***	0.52***	0.04ns	0.63***	0.43***
13	*A*	*I get sudden feelings of panic.*	0.68***	0.29**	0.56***	0.50***	0.06ns	0.34***
14	*D*	*I can enjoy a good book or radio or TV program.*	0.37***	0.67***	0.59***	0.22ns	0.57***	0.49***

Table 5.3. Correlations between items and HADS scale and subscales and in the written and visual forms. Each question is marked "D" if it belongs to the HADS-D subscale, or "A" if it belongs to the HADS-A subscale. *** = correlation significant for p < .001; **= correlation significant for p < 0.01; ns = correlation not statistically significant.

Table 5.4 shows the mean and standard deviation values divided by gender, class age, scale and subscales.

		Female			Male		
	Age:	0-35	36-55	56+	0-35	36-55	56+
Visual	Anxiety	1.07 (0.22)	1.14 (0.18)	1.07 (0.22)	1.15 (0.23)	1.26 (0.14)	1.22 (0.17)
	Depression	0.74 (0.23)	0.72 (0.25)	0.65 (0.19)	0.8 (0.17)	0.76 (0.17)	0.84 (0.25)
	General	0.9 (0.28)	0.93 (0.3)	0.86 (0.27)	0.98 (0.27)	1.01 (0.3)	1.03 (0.29)
Written	Anxiety	0.95 (0.3)	1.05 (0.23)	1.04 (0.25)	1.13 (0.24)	1.2 (0.19)	1.17 (0.13)
	Depression	0.88 (0.25)	0.85 (0.25)	0.84 (0.21)	0.94 (0.22)	0.97 (0.27)	0.99 (0.22)
	General	0.91 (0.28)	0.95 (0.26)	0.94 (0.25)	1.04 (0.24)	1.09 (0.26)	1.08 (0.2)

Table 5.4. Mean and SD scores for the written and visual HADS version, divided by gender and class-age. The "General" rows shows the mean and SD scores of the full questionnaire.

5.4 Discussion

Depression after stroke is common and persistent: a third of stroke survivors experience depressive symptoms (Hackett et al, 2014) with high risk of relapse, even after a long period of remission (Ayerbe et al., 2011). It is known to be related to substantial reductions in activities of daily living (Chemerinski et al, 2001; Lo et al, 2008; Schmid et al, 2011), and poorer QoL (Hilari et al, 2012), impairing physical rehabilitation and recovery (van de Weg et al, 1999; Nannetti et al, 2005).

Anxiety is also common after stroke: its prevalence estimates range from 18-38% (Campbell Burton et al., 2013) and, during the first 10 years after stroke, the cumulative incidence is 57% (Ayerbe et al, 2014). As for depression, it is persitent (Astrom, 1996) and

is associated with poor social functioning (Shimoda and Robinson, 1998) and low functional ability (D'Alisa et al, 2005).

Assessing mood disorders after stroke can be difficult, because about 30% of patients show aphasia (National Institute of Health, 2013) and reliable assessment of anxiety and depression after stroke, by clinical interview or by self-report questionnaires, can be impossible in the presence of language disorders (Aben et al, 2002; Berg et al, 2009). Indeed, to circumvent communication difficulties observer-rated tools were developed (Benaim et al., 2004, 2010; Watkins et al., 2001; Sutcliffe et al., 1998), even though correlations between observer-rated and self-reported mood scales have proven unreliable and, currently, no validated screening of post-stroke aphasic patients' mood disorders exist (Kneebone et al, 2012).

HADS is one of the most widely used questionnaires, in clinical and health psychology worldwide, both for screening purposes and assessment of symptom severity of mood disorders (Maters et al, 2013). In a review of 2002 by Bjelland and colleagues (2002), it has been found that HADS evidenced sensitivity and specificity as GHQ, and the correlation with other questionnaires for anxiety and depression, such as BDI (Beck et al., 1997), State Anxiety Inventory (Spielberger et al, 1970), Clinical Anxiety Scale (Westhuis and Thyer, 1989), and Symptom Checklist-90 (Derogatis, 1994), was between 0.60 and 0.80.

Since HADS is considered one of the most commonly used questionnaire to investigate mood disorders, we aimed to develop a visual form of this Scale, in order to perform its validation procedure on healthy subjects.

Our results suggested that the original HADS version proposed by Zigmond and Snaith (1983) and the visual HADS form realized for the purpose of this study, revealed the same structure for what concerns the splitting into two different categories of components ("positive" referred to the items with a positively valence, and "negative" related to those

with a negatively one), rather than into two subscales of anxiety and depression. Thus, the two HADS version seem to be equivalent in the Positive- Negative structure, but not in the Anxiety-Depression division.

Moreover, comparisons through Bayesian t-tests showed that the Anxiety scales in the two HADS forms are equivalent, while the comparison between the written and the visual Depression scales are different. Hence, only an equivalence between the HADS-A subscale of the original form and the HADS-A subscale of the visual form was found. This result may suggest that the pictures related to the HADS-A subscale are more able than those of HADS-D to represent the HADS items.

However, in our HADS visual form, a statistically significant difference between the HADS-A and HADS-D scubscales was found, while in the original written form (Zigmond and Snaith, 1983) this difference did not reach the decision boundaries. This result seems to propose that the HADS version developed by Zigmond and Snaith (1983) is not able to clearly discriminate between anxiety and depression, but it could be, more in general, a useful tool to assess the emotional distress. Indeed, a systematic review by Cosco and coll. (2012) on the structure of the HADS, demonstrated that the latent structure of this scale is still unclear, and depends on statistical methods employed. More specifically, 25 out of the 50 reviewed studies revealed a two-factor structure, 5 studies revealed unidimensional, 17 studies showed three-factor, and 2 studies revealed four-factor structures, underlying the HADS inability to consistently differentiate between the constructs of anxiety and depression, and suggesting that HADS use is more appropriate for the general measurement of distress.

On the other hand, our results reveal that HADS visual form is more able to distinguish between anxiety and depression than the original version (Zigmond and Snaith, 1983), even though we must be cautious in this conclusion, since it is necessary to administer the HADS visual form to aphasic patients with possible mood disorders.

In fact, the main limitation of this study is related to the sample, which consisted of only healthy subjects and not clinical population: next step will be the enrollement of post-stroke aphasic patients with possible mood disorders, in order to test the generalizability of the present results. It could be also important to diagnose the presence of anxiety and depression in the above mentioned clinical population, by administering other Scales assessing mood disorders, such as BDI (Beck et al., 1961), Beck Anxiety Inventory (Beck et al., 1988), or State Anxiety Inventory (Spielberger et al, 1970), to both evaluate the HADS visual version validation in the aphasic population, and test the validity of the Scale in differentiating anxiety from depression.

Despite this limitation and taking into account that our HADS visual form seems to discriminate between anxiety and depression, we could conclude that the HADS visual version shows interesting psychometric properties and it could be considered as a valid and useful tool to screen for mood disorders, especially in the aphasic population.

Given the persistent nature of post-stroke mood disorders, their clinical assessment and routine screening is higly recommended. The possibility to evaluate the presence of anxiety and depression in patients with severe language impairments, by means of a new tool able to circumvent their communication difficulties, could better address the treatment and the rehabilitation program, and also be clinically and cost effective.

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<u>Appendix 1</u> - Apathy Evaluation Scale, Clinician Version (AES-C) (Marin, 1996).

Name: _____ Date: _____
Rater: _____
Rate each item based on an interview of the subject. The interview should begin with a description of the subject's interest, activities and daily routine. Base your ratings on both verbal and non-verbal information. Ratings should be based on the past 4 weeks. For each item ratings should be judged:

Not at All Characteristic	Slightly Characteristic	Somewhat Characteristic	A Lot Characteristic
1	1	3	4

__ 1. S/he is interested in things.	+ C Q
__ 2. S/he gets things done during the day.	+ B Q
__ 3. Getting things started on his/her own is important to her/him.	+ C SE
__ 4. S/he is interested in having new experiences.	+ C Q
__ 5. S/he is interested in learning new things.	+ C Q
__ 6. S/he puts little effort into anything.	- B
__ 7. S/he approaches life with intensity.	+ E
__ 8. Seeing a job through to the end is important to her/him.	+ C SE
__ 9. He/she spends time doing things that interest her/him.	+ B
__ 10. Someone has to tell her/him what to do each day.	- B
__ 11. S/he is less concerned about his/her problems than her/him should be.	- C
__ 12. S/he has friends.	+ B Q
__ 13. Getting together with friends is important to her/him.	+ C SE
__ 14. When something good happens, he/she gets excited.	+ E
__ 15. S/he has an accurate understanding of her/him problems.	+ O
__ 16. Getting things done during the day is important to her/him.	+ C SE
__ 17. S/he has initiative.	+ O
__ 18. S/he has motivation.	+ O

Note: Items that have positive versus negative syntax are identified by +/-. Type of item: C = cognitive; B = behavior; E = emotional; O = other. The definitions of self-evaluation (SE) and quantifiable (Q) items are discussed in the administration guidelines [see Syllabus]. (Marin, 1991 [see References]) For self-rated and informant-rated versions of AES, the response options are Not at all true, Slightly true, etc. The Apathy Evaluation Scale was developed by Robert S. Marin, M.D. Development and validation studies are described in Marin et al., 1991 [see References]. Supplementary administration guidelines are available from the author.

<u>Appendix 2</u> - Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983).

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

<u>Scoring:</u>
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

Appendix 3- List of publications

Scientific articles published during the doctoral course:

1) D. Silvestro, E. Azicnuda, **M. D'Ippolito**, M. Giustini, R. Formisano, U.Bivona. *Beyond the classical psychotherapeutic setting to better provide support for caregivers of persons with severe acquired brain injury: some clinical evidence.* Journal of Psychology & Psychotherapy 2016; 6:2.
2) R. Formisano, E. Longo, E**.** Azicnuda**,** D**.** Silvestro**, M. D'Ippolito,** Truelle JL, von Steinbüchel N, von Wild K, Wilson L, Rigon J, Barba C, Forcina A, Giustini M. *Quality of life in persons after traumatic brain injury as self-perceived and as perceived by the caregivers.* Neurol Sci. 2017 Feb; 38(2):279-286.
3) R. Formisano, D. Silvestro, E. Azicnuda, E. Longo, C. Barba, J. Rigon, **M. D'Ippolito**, M. Giustini, U. Bivona. *Quality of life after brain injury (QOLIBRI): Italian validation of the proxy version. Intern. Emerg*. Med 2017 Mar;12(2):187-198.
4) **D'Ippolito M.,** Tramontano M., Buzzi M.G. *Effects Of Osteopathic Manipulative Therapy On Pain And Mood Disorders In Patients With High Frequency Migraine: a retrospective review of medical records.* J Am Osteopath Assoc. 2017 Jun 1;117(6):365-369.
5) D. Sattin, L. De Torres, G. Dolce, F. Arcuri, A. Estraneo, V. Cardinale, R. Piperno, E. Zavatta, R. Formisano, **M. D'Ippolito**, C. Vassallo, B. Dessi, G. Lamberti, E. Antoniono, C. Lanzillotti, J. Navarro, P. Bramanti, S. Marino, M. Zampolini, F. Scarponi, R. Avesani, L. Salvi, S. Ferro, L. Mazza, P. Fogar, S. Feller, F. De Nigris, A. Martinuzzi , M. Buffoni, A. Pessina, P. Corsico, M. Leonardi. *Care pathways models and clinical outcomes in Disorders of consciousness.* Brain and Behavior 2017; 7(8): e00740. doi: 10.1002/brb3.740.
6) Sattin D, De Torres L, Dolce G, Arcuri F, Estraneo A, Cardinale V, Piperno R, Zavatta E, Formisano R, **D'Ippolito M**, Vassallo C, Dessi B, Lamberti G, Antoniono E, Lanzillotti C, Navarro J, Bramanti P, Marino S, Zampolini M, Scarponi F, Avesani R, Salvi L, Ferro S, Mazza L, Fogar P, Feller S, De Nigris F, Martinuzzi A, Buffoni M, Pessina A, Corsico P, Leonardi M. *Analysis of Italian regulations on pathways of care for patients in a vegetative or minimally conscious state.* Funct Neurol. 2017;32(3):159-163.

7) C. Tassorelli, M. Tramontano, M. Berlangieri, V. Schweiger, **M. D'Ippolito**, V. Palmerini, S. Bonazza, R. Rosa, R. Cerbo, M. G. Buzzi. *Assessing and treating headaches and cranio-facial pain in neurorehabilitation.* J Headache Pain 2017; 18:99 doi:10.1186/s10194-017-0809-z.

Publications in Book Chapters:

1) Eva Azicnuda, **Mariagrazia D'Ippolito**, Daniela Silvestro. *Gli effetti diretti sulla famiglia del disturbo di empatia del paziente: esperienze cliniche*. Cap. 9 in: Umberto Bivona, Alberto Costa (a cura di). Empatia, danno cerebrale, ricostruzione del Sé. Ed. Armando Editore, 2017.

Scientific articles to be submitted to International peer-reviewed Journal:

1) **M. D'Ippolito**, G. Spinelli, M. Iosa, R. Formisano, S.M. Aglioti. *The role of apathy on conflict monitoring: a behavioral study on severe acquired brain injury patients using Flanker tasks.*
2) Canzano L.*, Scandola M.*, **D'Ippolito M.**, Buitoni C., Moro V., Aglioti SM. *A visual version of the Hospital Anxiety and Depression Scale (HADS): a preliminary validation study in healthy Italian population.* (*These authors equally contributed to this work).

Scientific articles recently submitted to International peer-reviewed Journal:

1) **M. D'Ippolito**, M. Aloisi, E. Azicnuda, D. Silvestro, M. Giustini, F. Verni, R. Formisano, U. Bivona. *Changes in caregivers lifestyle after severe Acquired Brain Injury: a preliminary investigation*. Brain Injury
2) R. Formisano, M. Iosa, F. Rizza, D. Sattin, M. Leonoardi, **M. D'Ippolito**. A new tool to assess responsiveness in disorders of consciousness (DoC): a preliminary study on the Brief Post-Coma Scale (B-PCS). Neurological Sciences.