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THE FRONTAL LOBES: EXECUTIVE AND BEHAVIORAL CONTROL OF HUMAN REASONING. IMPLICATIONS FOR UNDERSTANDING BRAIN INJURY

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Executive functions

Executive functions are higher-cognitive processes involved in planning, judgement, decision-making, anticipation or reasoning (Gallagher et al. 2003). They are responsible for the control of attention, concentration, inhibition, set-shifting and task management (Funahashi, 2001). The neuroanatomical locus of such processes is considered to be the frontal lobes, specifically the pre-frontal cortex, which over time has become synonymous with executive functioning. However it is well recognized that diverse neural circuitry, forming various frontal-subcortical networks and loops, are linked to the operation of the frontal lobes (Baddeley et al. 1997; Andres & Van der Linden, 2002).

Executive functions often refer to high-order functions operating in non-routine, novel and complex tasks encountered in real life situations, not easily surrogated or replicable in laboratory (Godefroy, 2003; Fortin et al. 2003). The term executive function defines complex cognitive processing requiring the coordination of several sub-processes to achieve particular goals (Elliott, 2003). Among them, working memory, prospective memory, strategic planning, set-shifting, abstract reasoning have been extensively investigated (Baddeley,1986; Cockburn,1995; Shallice & Burgess, 1991). Executive functioning is mediated by dynamic and flexible neural networks that neuroimaging studies have often inconclusively linked to specific and discrete prefrontal foci (Golby et al. 2001; Elliott, 2003). Structural or functional frontal pathology is associated with different aspects of executive dysfunction (Elliott, 2003). Further, many frontally-damaged patients may exhibit disturbed behaviour but their cognitive performance being not much impaired (Eslinger & Damasio, 1985). The relationship between clinical abnormalities of behaviour and cognitive deficits observed on formal testing has been examined. Some clinical disorders such as distractability and impulsivity were found to be related to attentional deficits (Baddeley et al. 1997). Burgess et al. (1998) demonstrated multiple correlations between neuropsychological tests of executive function (Card sorting tests, Trail Making, Verbal fluency) and some behavioural abnormalities (distractability, impulsivity, lack of self-control) assessed by a questionnaire. However many other behavioural disorders have not been linked to cognitive deficits and may be due to disorders of emotional control (Damasio, et al. 1991). Both focal and diffuse frontal lesions disrupt activities of daily living (ADL) and executive impairment could represent the main component of ADL failure (Eslinger & Damasio, 1985; Fortin et al. 2003). In particular, planning, self correction, decision making and judgement have been considered critical for ADL (Acker, 1990). Inattentiveness, mental slowing, impulsivity, lack of prospective memory, all contribute to the impairment in ADL of traumatic brain injury (TBI) victims, whose young age maybe has not allowed yet to "transfer" such routines into the "procedural" system, where the contribution of basal ganglia is essential (Fortin et al. 2003). The same authors refer to a "macrostructure" which includes strategic planning, procedural memory and working memory, being damaged following TBI. Consequently any multi-step requirement of real life, like a meal preparation or a recreational activity, could be grossly and permanently damaged. Meal preparation or going to the movie becomes a more difficult task than abstract problem solving or episodic learning during a testing session in the laboratory; certainly more "ecologically valid" and clinically more orienting. As outlined by Burgess and Shallice (1991), on cognitive testing the patient has to tackle a problem at any one time, the trials are very short, initiation is prompted and feedback is often given at the end of the task. Certainly it is not the same in real life situations, where the requirements are not clear, time constraints are internally generated, self-monitoring is hoped and feedback is an optional. Successful performance of patients with frontal lobe injury (especially TBI victims) on traditional paper and pencil tasks could be considered irrelevant since many of these tests do not explore strategic planning, competitive skills, or prospective memory. In contrast, preparing a meal requires prioritization along a temporal and hierarchical scale of demands and creativity involving maintenance of activity and drive (Fortin et al. 2003; Channon & Crawford, 1999).

A special mention deserves *working memory.* The human frontal cortex helps mediate working memory, a system used for temporary storage and manipulation of information that is highly involved in many cognitive tasks and complex cognitive activities (Baddeley, 2003; Smith & Jonides, 1999). It could be sub-divided into three systems, one concerned with verbal and acoustic information (the phonological loop), one providing its visual equivalent (the visuospatial sketchpad), and both of them dependent upon a third attentionally-limited control system, the central executive (Baddeley, 2003). A fourth sub-system, domain unspecific, the episodic buffer, has recently been proposed. Storage of verbal material activates the left-hemisphere supplementary and premotor cortex; storage of spatial information activates the right hemisphere premotor cortex; storage of object information activates other areas of the prefrontal cortex (Smith and Jonides, 1999). Using functional MRI Koechlin et al. (2000) report a functional double dissociation in executive functions within the frontal areas. Medial anterior prefrontal cortex, in association with the ventral striatum, was preferentially engaged when subjects executed tasks in expected or *internally generated* sequences, whereas the lateral prefrontal areas, in association with the dorsolateral striatum, was preferentially involved when subjects were asked to perform on tasks that were contingent on unpredictable or *externally driven* events. Medial and lateral prefrontal cortex are considered to belong to distinct architectonic streams. The medial stream is phylogenetically and ontogenetically older than the lateral (Stuss & Benson, 1986), considered well developed in the humans (Pandya et al. 1996). The ability to process contingent plans is more typical of the executive system. To adjust dynamically the sequential structure of on-going plans to new environmental demands, which may represent more evolved adaptive behaviour specific of human adults, is part of the exogenous plans where the lateral prefrontal cortex becomes preferentially involved, underlying motor and higher-order executive control and organization (Koechlin et al. 2003). Recently Gruben and Von Cramon (2003) revisited the functional neuroanatomy of working memory and conclude: 1) verbal and non verbal working memory systems refer to different domain-specific cortical networks; 2) there is a dual architecture of "verbal" working memory, represented by two partly dissociable systems, a left-lateralized premotor-parietal network underlying "verbal rehearsal" and a bilateral anterior prefrontal/inferior parietal network subserving non-articulatory maintenance of phonological information; 3) there seems to be no clear evidence of a neuroanatomical dissociation of the visuospatial working memory system, which rather relies on a bilateral posterior frontal involvement; 4) there seems to be very little evidence of a specific area of the brain preferentially triggered by the central executive system.

Finally, Faw (2003) has described a methaphorical conceptual framework of the prefrontal cortex that could be viewed as a "five-member" Executive committee:

- the "Perceiver" (ventro-lateral prefrontal cortex of the right hemisphere) which represents the frontal extension of the perceptual stream (world and self in object coordinates);
- the "Verbalizer" (ventro-lateral prefrontal cortex of the left-dominant hemisphere), which rather represents the extension of the language stream (world and self in language coordinates);
- the "Motivator" (medial -orbito-frontal cortex) which is considered the cortical extension of the subcortical amygdala stream (world and self in emotional coordinates)
- the "Attender" (dorso-medial prefrontal/anterior cingulate), the cortical extension of the subcortical extended hippocampal stream (world and self in spatiotemporal coordinates)
- the "Coordinator" (dorsolateral prefrontal cortex), the frontal extension of the dorsal perceptual stream, representing the world and self in high-level coordinates, controlling perception, attention, action and working memory.

Frontal lobes have long been considered to play a special role in the integration and regulation of complex human behaviour. Damage to these areas affect not only high level cognitive functions but also personality, social behaviour, self-awareness (Alexander et al., 1979; Damasio, 1994). Over the last ten years there has been a great change in the interpretation of the role of frontal lobes within the brain. Neuroimaging has contributed more than any other field to understand the contribution of different areas of this region to the final behaviour, either in normal subjects or following pathological conditions. "Theory of mind" is an emerging term that refers to the development of a special human faculty, the awareness of one's mental state and the likely content of other people's minds (Stuss et al. 2001; Frith & Frith, 1999). Several brain regions have been proposed for a special role in "theory of mind", particularly within the right hemisphere. Damage to the right hemisphere impairs the non-linguistics aspect of communication, empathy and pragmatics; it reduces the ability to understand sarcasm, jokes, irony, various aspects of the human behaviour which require inference and metacognitive reasoning (McDonald, 1993; Siegal et al., 1996; Stuss et al. 2001; Eslinger, 1998). Orbito-frontal cortex has been specifically implicated in "theory of mind" (Baron-Cohen, 1999; Frith & Frith, 1999), including the superior temporal sulcus and the amygdala. Executive functions and "theory of mind" seem correlated, at least in children behaviour (Frye, 1995) however, according to Hughes (1998) executive function performance helps predicting theory of mind performance, but not vice versa. It may be the case that regions of the brain that regulate theory of mind and executive functions are anatomically proximal. Fine et al. (2001) have recently proposed that the neurocognitive system mediating theory of mind is developmentally separable from the neurocognitive system mediating executive functions and that executive functions can operate independently from theory of mind. Bilateral, particularly right orbito-frontal lesions might impair patients' capacity to incorporate other people's feelings and experiences into their own plans of action, failing to activate relevant somatic markers from past emotional experience and reducing the ability to guide their response options (Bechara et al. 1997; Bechara, 2002). Guessing becomes the preferred response modality, a method of approximation and intuition predominantly related to the orbito-frontal brain region, in the right hemisphere (Elliott, 1999). This very region is critical for self-regulated social and cognitive behaviours, regardless of performance on standard IQ measures or traditional frontal lobe testing (Eslinger & Damasio, 1985). The frontal lobes are essential, and the right frontal circuits perhaps particularly critical, maybe because of their central role in the neural systems implicated in social cognition, in feelings' inference and empathy as well as in attentional control, emotion, motivation and behavioural regulation (Stuss et al. 2001).

Personality and behavior

We are biological creatures, born to live and die, to organize complex forms of interaction. At times caring for others, creating ideas, objects, forms of better living; at times cruel, destructive, able to hate and kill (Perry, 2002).

Humans are the product of "nature" (genes) and "nurture" (experience). Genes and experience are interdependent. Genes are chemicals and, without experience, create nothing. Experience, without a genomic matrix, cannot create, regulate or replicate life in any form (Perry, 2002). The brain is the product of neurodevelopment, a long process of micro-construction that requires several steps, the last of which is "myelination". The Frontal areas of the brain are the last areas to myelinate usually into adolescence and after (Kolb & Whishaw, 1990; Fuster, 2002). Neurodevelopment is "sequential", from the least organized to the most organized areas of the neural substrate, regulating the most complex and integrated forms of behaviour. Frontal cortex represents the highest level of all neural structures, regulating executive behaviour as well as initiating and maintaining sociality (Cory, 2002). The frontal cortex represents 1/3 of the totality of the neocortex (Fuster, 2002). It is an extensive area of complex behavioural regulation and integration, a neural crossroad for multimodal distributed processing of incoming and outgoing information (Mesulam, 2001).

The late maturation and late myelination of its complex connections go in parallel with the development of cognitive functions. The association cortex of the frontal lobe, commonly called pre-frontal cortex, is in charge of the temporal organization of behaviour, speech and thinking (Fuster, 1999). Pre-frontal cortex also seems to regulate initiation, planning, problem solving, working memory, attention, impulse control, self-perception, social adaptation, inexstricably linking areas associated with cognitive and emotional processes (Barbas, 2000). The differential role of the pre-frontal cortex still remains poorly understood. Recently however, different parallel networks have been described (Allegri & Harris, 2001). Three of these circuits are the most relevant to understanding of behaviour:

- 1. the *Dorso-lateral* prefrontal circuit, that mediates cognition and executive behaviour. It is represented by the late-maturing areas of the frontal convexity and it is principally involved in higher level attentional, mnestic and abstract reasoning activities;
- 2. the *Orbito-frontal* circuit, mediating social and emotional behaviour. It is primarily linked with the early-maturing areas of the basal frontal brain, mainly involved in expression and control of emotional and instinctual behaviours;
- 3. the *medial frontal* circuit involved in motivation, initiation and maintainance of

behaviour (Allegri and Harris, 2001; Fuster, 2002; Barbas, 2000).

The comprehensive assessment of a frontal lobe injury is one of the most complex problems in diagnosis and treatment due to the variability of the nature, extent and effect of various neurological disorders (Quester & Klug, 2003). Damage to the frontal cortex then impairs a variety of skills, abilities and behaviours such as planning of daily activities, reasoning, concept formation, maintaining information in working memory, associative and strategic learning, metacognitive thinking, social skills, moral beliefs, personality traits, and even "theory of mind", a special faculty of the human brain which has to do with the interpretation and appreciation of other people's feelings and mental states (Stuss, et al. 2001; Fine et al. 2001). Frontal lobe damage can lead to dramatic alterations of conduct, personality, psychosocial integration, at times leaving most cognitive and sensory-motor functions relatively intact (Mesulam, 1986). From a clinical standpoint there seems to be a spectrum of symptoms rather than definite syndromes. Some patients become puerile, profane, facetious, irresponsible, irascible, aggressive, overly abusive; they become *dys-inhibited*. Others lose spontaneity, initiative, curiosity, develop apathy, inertia, slowing of action and mentation, they become *abulic*. Still others show lack of insight and planning, loss of creativity and spontaneity, jump to premature conclusions and become excessively stimulus-bound and concrete (see Mesulam, 1986). The "frontal syndrome" then seems an "umbrella term" under which we cover all cognitive, behavioural, personality changes after a frontal damage. It seems overtly difficult to disentangle each aspect of this complex human behavioural organization, the resulting clinical profile being directly related not only to size, extension, side and temporal course of the injury which have received more attention from authors in the past, but rather and specifically by the "nature", "time in life" and "severity" of the injury.

Traumatic brain injury is not a disease entity. The risk of head trauma is higher for younger populations whose brain structures have not yet reached complete maturation of complex connectivity. Traumatic brain injury follows the rules of physics. Pre-frontal and temporal-polar areas of the brain are more often damaged due to the physical and mechanical forces released following TBI, not necessarily regulated by vascular supply or other metabolic laws. Acute, disruptive shearing and stretching forces, which follow specific anatomical directions, diffusely

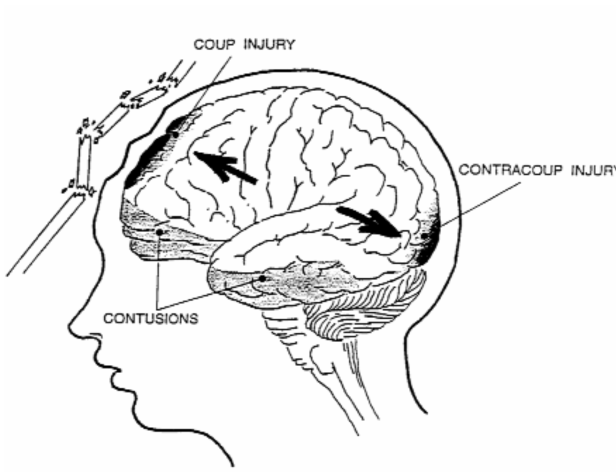

Fig. 1: Mechanism of injury following TBI.

disrupt connections between axons, vessels membranes, etc. generating a cascade of events that has no comparisons in neuropathology. Traumatic brain injury is poorly understood because escapes most of the known pathophysiological mechanisms. The "area of impact" is the zone comprised within the anterior part of the medium fossa (tip of the temporal lobe) and the rostral ventral aspect of the frontal lobe (*orbito-frontal* area) by mechanisms of shearing and stretching fibers/axons against the base of the skull.

This is an area of the brain without anchorage, which easily fluctuates under the cone of pressure and under physical forces due to the impact, usually along the same lines, but with different intensity and severity, directly related to the dynamic of the injury. Final damage, at least primary damage, varies according to the intensity of the coup, the resulting countercoup, the angular and rotational forces that lacerate the brain tissue centrifugally, from the midline sagittal aspect of the anterior-inferior areas (medial and orbital cortex impacting against the lamina cribrosa and the roof of the orbit as well as against the wing of the sphenoid bone) toward the surface of the cortex (frontal convexity) and the deep connections with the striatum. TBI clinically resembles degenerative disorders such as dementia (diffuse damage to associative areas) but it is not progressive and does not affect all areas of cognition. Unlike strokes, only rarely the injury is restricted to the pre-frontal convexity or incapsulated within the areas of the lenticulo-striate arteries (subcortical; internal capsule). It might share similarities with mental retardation; however it does not affect the posterior associative areas and general knowledge is often preserved (except for children traumatic brain injury which deserves a different coverage). Finally, traumatic brain injury patients seem psychotic subjects but yet they do not have a "full" history of psychosis and the matrix of their disturbances is clearly and uncontrovertibly "organic". In other words TBI causes a functional disruption and disconnection (most times irreversible) of brain areas which (when maturation has been completed) coordinate, regulate, filter and organize all aspects of behaviour, including high level cognitive, psychosocial and interpersonal. The resulting clinical repertoire seems related to the nature of the injury, the physical characteristics of the injury itself and the dynamics of the impact. Traumatic brain injury often affects the brain during the last phase of maturation; basic skills have been already developed; general knowledge has been usually organized (except for children TBI), but myelination of prefrontal areas has not yet been completed, since most of the victims are into their adolescence. TBI then affects a very "crucial zone" of behavioural regulation, which has not yet reached full maturation. The recovery pattern that we describe then needs to account for the fact that most behaviours are "NOT" lost, but not yet developed, not yet fully organized. Assessment then, including neuropsychological testing, is often inappropriate at least for 3 reasons: 1) the very behaviours that we intend to examine are not yet fully developed; 2) most aspects of the tested behaviours, skills or abilities are not easily separable from each other; 3) our testing procedures are very far from "real life" situations and commonly investigate finite aspects of the cognitive/behavioural panorama. Presumably these, among others, are aspects to consider before reaching diagnostic conclusions and before formulating definitive prognostic or treatment plans. Injury mechanisms seem to be restricted in most cases around the ventral and mesial (more sagittal) aspects of the pre-frontal cortex and the temporal pole, including the mildest forms of TBI (which represent the highest proportion of all cases), with resulting high-order, behavioural-executive disturbances which often affect personality, psychosocial and emotional aspects of behaviour without major sensory-motor nor attentional/mnestic or linguistic breakdowns. More severe injuries involve and disrupt more subcortical and convexity areas of the pre-frontal cortex and cognitive-executive disturbances of attention, working-memory, perception, visual organization, problem-solving and strategical learning become more salient.

Following this strictly clinical and pathophysiological interpretation then, we expect most individuals with milder forms of TBI to receive damage to the medial and orbital zone of the frontal lobes. We expect them to present with long-lasting behavioural, personality and psychosocial disturbances which affect the "quality" of their performance in the real world, with significant difficulties in psychosocial re-integration, community re-entry and final adaptation to the compelling and challenging requests of the real world. This is true for at least 70% of the entire TBI population.

The resulting spectrum of symptoms seems not to be a collection of disturbances and deficits appearing at random from an array of possible disturbed behaviours. It seems rather a rational and expected "hierarchy" of clinical symptoms mainly regulated by intensity and severity of the injury (the rules of physics) along a "gradient" of disturbances. Behavioral, personality, psychosocial disturbances are then more common at least for two reasons: 1) the dynamic of the injury very often involves the frontal and temporal areas of the brain which regulate all high order interpersonal skills and emotional-coping abilities at least for 70% of the victims (all milder forms of TBI); 2) these very abilities and behaviours have not yet fully completed maturation, since most of the victims are still into their adolescence.

A final comment deserves the Orbito-frontal cortex, emerging from relative obscurity to assume a fundamental role in behavioral neurosciences (Eslinger, 1999). Traumatic forces are more extensively (but relatively) localized to this area of the frontal lobes, without respecting the artificial separation of different frontal areas, whose contribution has often been accumulated *in vitro* within surrogated environments using reductionistic experiments. The resulting disturbances following TBI are infact more often behavioural, with major personality disintegration, coping disturbances and impulsive control of behaviour. Most TBI victims manifest a "Dys-inhibited syndrome profile", typical of the mild or moderately severe brain injury where lesions are most often restricted to the ventral-rostral-mesial (orbito-frontal) cortex. They are egocentric, childish, stubborn, tactless, aggressive and abusive. As injury becomes more severe and traumatic damage extends toward the more lateral surface of frontal convexity or to more deeper nuclei of the striatum and their connections, symptoms assume more an "abulic syndrome profile" (Trexler and Zappalà, 1988; Zappalà, 2000). Patients show disinterest, lethargy, reduced drive and lack of initiative. Between the two, needless to say, there are a countless number of different clinical profiles, secondary to differential patterns of severity, dynamic of the injury, premorbid personality and premorbid biological risk, different complications, etc.

The complexity and level of reached neurodevelopment at the time of the injury (mainly correlated with the age of the victim) represents a crucial argument for integrative interpretation of the final clinico-pathological picture following traumatic brain injury.

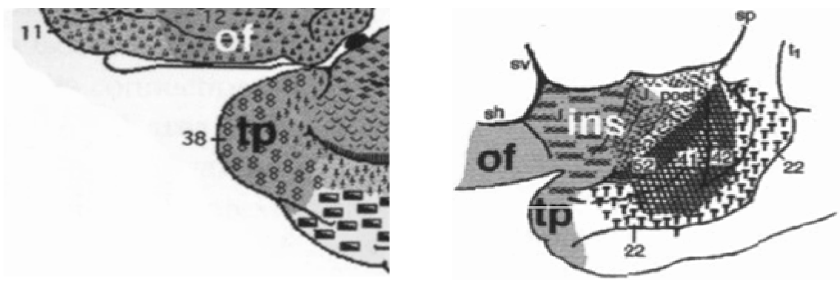

Fig. 2. Orbitofrontal area (mesial and lateral views).

The Orbitofrontal region of the brain remains a crucial area for understanding complex HUMAN behaviour; it is the mostly damaged brain area following TBI; it also represents the least understood area of human brain and yet the least accessible brain area to clinical as well as instrumental investigation. Damage to this area of the brain causes serious barriers to community and vocational re-entry, as well as adaptive functioning in a complex, competitive and ever-challenging world (Satish et al. 1999).

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