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Dissociations of Memory Processes: The Contribution of Research on Memory Impairment Following Traumatic Brain Injury (TBI)—A Focused Review

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Abstract

Objective: Deficits in memory and learning skills are frequently reported following traumatic brain injury (TBI). The goal of the present focused review is to present memory studies of moderate-to-severe TBI that found, within the same sample, that one memory component is preserved, while another is impaired, demonstrating a dissociation. By reviewing these studies, we would like to claim that the breakdown of memory processes following TBI could unmask underlying sub-processes and components that seem inseparable in intact memory. **Methods:** The search criterion for this focused review was studies of memory functions following TBI (mostly moderate-severe) that reported on dissociations of various memory processes within the same sample, so that one process was impaired while another was preserved. **Results:** We found studies that adhered to the search criterion in several domains of memory: Working memory, episodic memory, verbal learning, priming, contextual memory and visual search. **Conclusions:** Characterization of the memory breakdown following TBI could contribute not only to the assessment and rehabilitation of this population but also to our understanding of the composition of intact memory system. These studies, although presenting a single dissociation, can still contribute to the validation of several dissociations introduced in the memory literature.

Keywords

Learning and Memory, Head Injury, Traumatic Brain Injury

1. Introduction

Understanding brain-behavior relationships, on the one hand, is dependent on the study of brain structure and function, and on the other hand, depends on the analysis of behavioral and cognitive processes. Brain imaging tools, with their ongoing technological advances, have led to significant improvements in spatial and temporal resolution of neural processes, as measured by fMRI and MEG. The analysis of behavioral and cognitive processes is led by cognitive psychologists and cognitive neuroscientists, using sophisticated experimental tasks. Thus, the advancement of our understanding of brain-behavior relationships is dependent on the careful study of both sides of the equation, brain as well as behavior. This study focuses on the behavioral part, by presenting studies showing dissociations within memory processes that led eventually to better understanding of brain-behavior relationships.

Memory impairments following traumatic brain injury (TBI) are studied primarily because of their clinical and rehabilitative implications. The careful analysis of memory functions is paramount to the functional assessment and is essential to building a rehabilitation plan for this patient population. One may argue that because of the injury's diffuse nature, this patient population is not an ideal group to study brain-behavior relationships. In this paper, we would like to propose that the study of memory impairment following TBI, in addition to its clinical implications, could indeed contribute, theoretically and conceptually, to the understanding of memory processes' structure and function. More specifically, we would like to argue that despite Teuber's (1955) recommendation on the double dissociation approach to study of the brain, single dissociations can reveal important insights into the component parts of complex cognitive processes (such as various aspects of memory), and therefore deserve close attention as part of understanding brain-behavior relationships. The goal of the present focused (but by no means exhaustive) review is to present memory studies with moderate-to-severe TBI that found, within the same sample, a dissociation between various aspects of the memory process. This dissociation was based on the finding that one aspect of memory is preserved while the other is impaired following the injury (this was the search criterion). Furthermore, we are less concerned with the question of whether these reports are consistent with the rest of the literature. Because of the diffuse nature of TBI, the heterogeneity of patient groups and the great variety of tests and procedures administered, findings are not always consistent. For the purpose of the present study, any dissociation reported could serve as proof that memory processes are dissociable. One more clarification is in order: because of the diffuse nature of TBI, we have no intention of associating a particular component of memory dissociation with a specific brain structure. Nevertheless, in the discussion section we will raise the hypothesis that the frontal lobes, known to be frequently compromised following TBI (Avants et al., 2008; Bigler, 2013; Kinch & McDonald, 2001), are good candidates to subserve some of the impaired memory processes reported.

In his seminal paper, Jacoby (1991) presented his "process dissociation" methodological approach, which suggests that "process" is unequal to "task". In other words, it is assumed that a cognitive task is composed of several cognitive processes. The challenge of the cognitive scientist is to break down the task into its components, in order to reveal the underlying cognitive processes. For example, this goal can be achieved by various cognitive manipulations such as divided attention, where some aspects of the task would not be affected by it (i.e., automatic processes), while others will (i.e., controlled processes). The cognitive neuroscientist might use a different approach: he or she may study patients with a particular brain disorder, looking for a sparing of one aspect of the task and an impairment of another. Thus, the cognitive manipulation of the task or the differential breakdown of memory processes in patients would suggest that different aspects of the task are dissociable and are probably mediated by different brain regions.

In the context of neuropsychological assessment, the Boston process approach (Milberg et al., 2009) made a very similar assertion, namely, not to equate a "test" with a "process". As demonstrated by these authors, the study of the test performance process (e.g., Block design subtest of the WAIS and the Rey-Complex figure test), rather than looking only at the final score, reflects the impaired cognitive process, and leads to a conclusion of whether a right or left hemisphere dysfunction is present. Such a detailed neuropsychological evaluation, aimed at resolution of the cognitive process, is critical for making predictions about daily life performance following brain injury (for review, see Vakil, 2012). Thus, this approach illuminates the clinical implications of dissociations demonstrated in the memory research on individuals who have sustained TBI.

Thus, the "process dissociation" framework (Jacoby, 1991) and the "Boston process approach" (Milberg et al., 2009) teach us that in order to study the brain-behavior relationship successfully, either in the context of brain research or neuropsychological assessment and rehabilitation, it is not only important to refine the resolution of our brain activity measurement tools, but also to sharpen resolution of the cognitive processes being tested.

2. Neuropsychology

The history of neuropsychology has been characterized by repeated attempts to relate brain regions to cognitive functions, and over the years has led numerous researchers to employ various techniques toward this end. Many of the animal and human lesion studies were aimed at localizing various cognitive processes and functions in the brain. As argued above, the dissociation of a cognitive process is critical for the study of brain-behavior relationships. Just like a prism, where a spectrum of colors is revealed when a white light is projected through it, a system such as memory may appear to be a unitary structure but can be broken down into a number of processes and components.

Concurrently with the lesion studies, cognitive psychologists such as Jacoby

(1991) attempted to study the fine architecture of cognitive processes. The early cognitive psychologists focused primarily on input-output or stimulus-response relationships, treating the brain as a black box. The dissociation of different memory processes was demonstrated by differential responses to various learning conditions manipulations (e.g., divided attention, exposure time, and depth of processing) or retrieval conditions (e.g., time delay, context or modality change).

Since the development of the cognitive neuroscience discipline, a great effort has been made to validate memory dissociations using cognitive manipulations and relating them to respective brain regions. This was accomplished either by studying patients with localized brain lesions or by utilizing neuroimaging techniques. However, efforts to associate a given cognitive function with a localized brain region, based on head injured patients, have been met with criticism. Hans Lukas Teuber (1955) claimed that a single (or simple) dissociation, in which a lesion to a particular brain area ("A") causes impairment to one task ("a") and not to another ("b"), could not be taken as a sufficient indication that area "A" exclusively subserves task "a". As Dunn and Kirsner (2003) put it, the reason is that the preserved task may possibly be less sensitive than the impaired task to the injury in that particular region. Therefore, Teuber introduced the concept of Double Dissociation, which requires that not only damage to area "A" affects task "a" and not task "b", but in addition it should be demonstrated that a lesion to area "B" affects task "b" and not task "a". Thus, a double dissociation indicates that the two dissociated tasks rely on two separate cognitive modules, and possibly two distinct anatomical brain regions. The double dissociation may also suggest that there are at least two processes, networks, linkages, nodes, or thresholds (Gurd & Marshall, 2003). Yet a single dissociation is valuable as well, because it could at least indicate that two tasks are dissociable (Baddeley, 2003). Furthermore, the two examples that we provide below demonstrate how single dissociations serve as building blocks for some of the well-established double dissociations that exist in amnesia.

The dissociation between short- and long-term memories in amnesia

One of the phenomena used to demonstrate the dissociation between short- and long-term memory was the Serial Position Effect (Glanzer & Cunitz, 1966). In a test of immediate recall of a word-list, the typical finding is that words from the end of the list are better recalled (i.e., recency effect) than words from the beginning of the list (i.e., primacy effect), while words from the middle of the list are the least recalled. Ellis and Hope (1968) demonstrated that manipulating the presentation rate (3 words vs. 9 words per second) affected the primacy, but not the recency effect. In contrast, manipulation of time delay of recall (immediate vs. 30-second delay) affected the recency but not the primacy effect. This double dissociation led researchers to conclude that primacy and recency effects reflect different memory processes or stores. These studies were among the first to demonstrate that memory is not a unitary construct but is composed of several processes and components.

In contrast to the clear cognitive demonstration of a full double dissociation between short- and long-term memory, for a long time the study of amnesia was only able to show a single dissociation. For example, Baddeley and Warrington (1970) with six amnesic patients, demonstrated that when tested with free recall of a word list, the amnesic patients showed a preserved recency effect and an impaired primacy effect. Their interpretation of this finding was that the amnesia affected long, but not the short-term memory, demonstrating a single dissociation. The double dissociation in individuals with memory impairment was completed by Shallice and Warrington (1970), who studied a patient (K.F.) with damage to the left cerebral cortex who presented the mirror image of amnesia, that is, impaired short-term memory and preserved long-term memory. But further studies of amnesic patients have pointed to more memory dissociations, as described below.

The dissociation between declarative and procedural memory in amnesia

The reports by Milner (1959) on the classical amnesic patient H.M. were the first to point to the association of mid-temporal lobe areas (MTL), and the hippocampus in particular, with memory functions. The only dissociation presented at that time was between H.M.'s preserved intelligence and his memory, which was severely impaired. The next phase was when a (single) dissociation was reported between declarative (knowing that) and procedural (knowing how) memory. Declarative memory was severely impaired following MTL lesions, but procedural memory was preserved (Cohen & Squire, 1980). Later, studies reported impairment of procedural memory following dysfunction of the basal ganglia in patients with Parkinson's disease (again, a single dissociation) (Jackson et al., 1995; Pascual-Leone et al., 1993). These findings were succeeded by an additional single dissociation between impaired procedural learning and preserved declarative learning in patients with Parkinson's disease (Vakil & Herishanu-Naaman, 1998). The full double dissociation was reported by Knowlton et al. (1996). They tested amnesic patients, patients with Parkinson's disease and healthy controls on procedural and declarative memory tasks. The procedural task was the "Weather Prediction" task, which is a probabilistic judgment task. In this task participants learned implicitly to predict one of two outcomes (Sun or Rain) based on the particular combination of cues. The declarative task consisted of multiple-choice questions about cues from the task. It was found that, unlike control and amnesic patients, patients with Parkinson's disease had difficulties in learning the probabilities underlying the task. In contrast, when declarative aspects of the task were tested, performance of the amnesic patients was impaired, as compared to that of controls and patients with Parkinson's disease. The researchers interpreted this double dissociation to indicate that while damage to the basal ganglia (i.e., patients with Parkinson's disease) affects procedural memory but not declarative memory, damage to the MTL regions (i.e., amnesic patients) affects declarative but not procedural memory. This double dissociation was confirmed by neuroimaging studies (e.g., Poldrack & Packard, 2003).

These two examples with amnesic patients illustrate the dynamics and the phases in the development of our understanding of brain-behavior relationship. It is evident that reports on single dissociation paved the way for the later discoveries of double dissociations between long- and short-term memory and between declarative and procedural memory, sub-served by the MTL and basal ganglia regions, respectively.

Memory impairment following traumatic brain injury (*TBI*)*—examples of single dissociations*

As discussed above, single dissociations paved the way for the discovery of double dissociations, enabling us to expand our understanding of brain-behavior relationships. As noted, due to the heterogeneity of TBI patient groups and the great variety of tests and procedures administered, findings of these studies are inconsistent. But for the purpose of the present study, any dissociation reported might serve as proof that memory processes are dissociable. For that reason, we only report dissociations demonstrated within the same study with the same sample of patients with TBI.

The wealth of research on the effect of TBI on memory has been reviewed in several papers and book chapters (Azouvi et al. 2017; Canty et al., 2014; Sander et al., 2018; Vakil, 2005, 2013). It is clear from reading the literature that a wide range of memory functions is significantly impaired following TBI. Memory difficulties are among the most frequent complaints made by patients who sustained TBI (Rabinowitz & Levin, 2014). Memory impairments are also the most frequent residual deficits following TBI (Levin, 1989). Memory functions following TBI have a longer recovery rate than other cognitive functions (extending even ten years post injury, Zec et al., 2001). The severity of memory impairments is also predictive of recovery after TBI, as reported by Allanson et al. (2017). Therefore, it is not surprising that these deficits are the most widely investigated cognitive domain in patients with TBI (Goldstein & Levin, 1995).

Could memory research with patients following TBI contribute to our understanding of memory processes, despite the diffuse nature of the injury? We would like to argue that due to the diffuse nature of the injury, finding a double dissociation is very hard in this population, yet finding a single dissociation is possible. As argued above, a single dissociation is a necessary step towards finding a double dissociation. In the next section, we will present studies carried out on patients with TBI, testing various aspects of memory, in which a single dissociation was demonstrated within the same group of patients.

Working Memory: *Central Executive vs. Slave Systems*

Working memory (WM) is the system responsible for holding and manipulating information online (Baddeley, 2003). The research on WM in individuals with TBI demonstrates a single dissociation, albeit with inconsistent results. This dissociation is based on Baddeley's multi-component model of WM. The major components of this model are the "central executive" and the two slave systems, the "phonological loop" and the "visuospatial sketchpad". In the revised version of Baddeley's WM model, the episodic buffer component was added. The central executive is responsible for controlled and attentional processes, divided attention and manipulation of the information. The slave systems are modality specific systems, responsible for the maintenance and rehearsal of the information. Vallat-Azouvi et al. (2007) demonstrated that patients with severe TBI performed similarly to controls on tasks tapping the slave systems, i.e., the phonological loop (e.g., digit span) and the visuospatial sketchpad (e.g., visuospatial span using the Corsi Block-tapping test). In contrast, these patients were impaired on a variety of WM tests (e.g., the Brown Peterson paradigm), particularly under conditions of interference. These findings point to central executive dysfunction.

Thus, this study is an example of a single dissociation of memory in individuals following severe TBI. The findings that performance of the slave systems was not affected by the brain injury and that performance of the central executive was affected, could be viewed as support for the dissociation introduced by Baddeley (2003) in his multi-component model of WM. It is important to emphasize that the brain regions associated with the various components of WM cannot be derived from these findings.

Long term memory: *Episodic vs. Semantic Memory*

Episodic memories are memories of a specific event, time and place. Hence, these memories are highly context dependent. Semantic memory refers to memories or knowledge that is context-free, i.e., facts, general knowledge and information (Tulving, 1972). Knight and O'Hagan (2009) presented patients with TBI with names of various persons. In the first task, they had to recognize which names relate to famous people. The recognition of famous persons presumably tested their semantic memory (did they know who the person was). The second task related to the recall of a context-related memory associated with this person, an episodic memory task (could they relate the person to a specific time and place). There was no difference between individuals with TBI and controls in name recall. However, there were significant differences in the ability of the two groups to generate autobiographically significant memories of the famous persons; these memories contain contextual information about a specific episode (Knight & O'Hagan, 2009). These results were confirmed in other studies on individuals with TBI (Esopenko & Levine, 2017; Rasmussen & Berntsen, 2014, but see Roberts et al., 2018). Again, we encounter a single dissociation of memory following TBI.

The Learning Process: *Acquisition vs. Retention*

Other dissociations relate to the most fundamental processes of learning. DeLuca et al. (2000) investigated whether individuals with TBI have deficits in the acquisition and retention of relatively simple information, such as a word list. In their study, they discovered that patients with TBI needed more repetitions in order to reach the pre-specified learning criterion. After reaching this criterion, the TBI group and the healthy controls did not differ on delayed testing (30 and 90 minutes later) and their forgetting rate was similar. These results indicate that patients with TBI initially remembered fewer words than the controls. However, when given additional learning trials to ensure that they acquire the same amount of words as the control group, similar retention and forgetting rates were observed in both groups. The fact that patients with TBI require more repetitions during acquisition, points to a deficit in acquisition but not in retention; their forgetting rate is similar to that of the controls. Wright, Schmitter-Edgecombe, and Woo (2010) reached a similar conclusion based on word list memory (i.e., California Verbal Learning Test) of individuals with TBI. The conclusion is that deficient encoding is the primary cause for the subsequent retrieval impairment. Thus, although it is a single dissociation, this finding validates the dissociation between acquisition and retention processes.

The Learning Process: *Omissions vs. Additions*

Learning rate relates to the degree of improvement over several trials of repeated presentations of stimuli (e.g., words, pictures). The Rey-Auditory Verbal Learning Test (AVLT), a supra-span learning and memory task, can be used to analyze verbal learning rate (Vakil & Blachstein, 1997). Using the Rey AVLT, patients with TBI showed a slower rate of learning, indicating that they benefited less from repeated learning experiences, in comparison to controls (Blachstein et al., 1993). This finding raised the question, what is the source of this slower learning? Blachstein et al. (1993) suggested distinguishing between *additions*, which is the number of new words added from trial to trial, and *omissions*, the number of words recalled in a previous trial and not recalled in the current trial. Thus, the increment in the number of words from trial to trial is the total of number of new words added minus the number of words omitted. When the learning rate was broken down into additions and omissions, it was found that the group with TBI did not differ in the amount of words added from trial to trial. However, the amount of words omitted from trial to trial was significantly higher for the group with TBI. More specifically, while in the control group an average of one word was omitted from trial to trial, the group with TBI started by omitting an average of a word and a half, and by the fifth block, three words were omitted. This pattern of higher turnover of words in the group with TBI was interpreted as reflecting difficulty in transferring words from short to long-term memory. This dissociation was confirmed in other populations, such as young children and older adults, both groups showed higher rates of words turnover (Blachstein & Vakil, 2016).

Priming: *Conceptual vs. Perceptual*

Priming effect is evident when prior exposure to stimuli facilitates its subsequent processing, as measured by either speed or accuracy. Several researchers have distinguished between perceptual and conceptual priming, based on the level of processing effect on various tasks (Srinivas & Roediger, 1990; Blaxton, 1992; Challis & Brodbeck, 1992). Conceptual, but not perceptual priming could benefit from a deeper processing of information.

Examples of *perceptual* priming tasks are "Perceptual Partial Word/Picture Identification". In such a task, either words or pictures are presented, starting from the most degraded form to the most complete drawing of the object or the word. Participants are first asked to identify the stimulus in its most degraded form. Evidence of priming effect exists when upon repeated exposure to the stimuli, these words or pictures are identified at an earlier stage, which is in a more fragmented form than in the previous exposure. Schacter and Buckner (1998) showed that participants with MTL amnesia were quicker to identify previously seen images than novel ones, even though they did not recall seeing these images earlier. This finding indicates that perceptual priming effect is preserved in amnesic patients with MTL lesions.

An example of *conceptual* priming is the Category production task, used by Roediger and Blaxton (1987) in individuals with MTL amnesia. Participants were given five items in three different categories (i.e., occupations, transportation or vegetables). Four of the items in each list are conventional examples of occupations, such as an architect, a lawyer, or a doctor and one was rarer, such as a glass cutter. When asked to recall the list of occupations (or other category) that was presented to them earlier, patients with MTL amnesia were severely impaired. However, when asked simply to list types of occupations, they listed mostly conventional occupations, but also included the rare occupation that was presented previously (in this case, a glass cutter). Each of these studies indicate that both perceptual and conceptual priming are intact in amnesic patients, pointing to a well-functioning implicit memory system.

The fact that patients with MTL amnesia perform within normal limits on both tasks shows that perceptual and conceptual priming are not well differentiated. However, Vakil and Sigal (1997), in their study conducted on patients with TBI, found support for the dissociation between perceptual and conceptual priming. Vakil and Sigal tested 24 patients and 24 matched controls on a perceptual priming task (i.e., perceptual partial word identification) and a conceptual priming task (i.e., category production). It was found that patients with TBI performed poorly on the conceptual priming tasks but performed just like the controls on the perceptual priming task. In addition, the TBI group did not benefit from deeper encoding prior to the test. This is another example in which a study with patients following TBI provides support for a single dissociation between two cognitive processes.

Context Memory: Source Memory vs. Context Effect

We are surrounded by multiple stimuli, some of which are of greater importance to us than others and are thus at the focus of our attention. Other stimuli serve as the background, or context, for the salient stimulus. The important role of context in memory processes has been recognized for many years. A context effect (CE) is said to occur when memory performance is improved by the presence of the original contextual stimuli. CE has been widely documented in the human memory literature (Memon & Bruce, 1985; Vakil et al., 2007). CE can be viewed as an implicit measure of contextual information because its presence improves the memory of target information without asking explicitly to retrieve that contextual information. In contrast, Source Memory is the memory of contextual information when asked explicitly to be retrieved (Janowsky et al., 1989). Thus, asking about the temporal order or the spatial location of words presented at the study phase would be a measure of source memory. But the improved retrieval of words when the original temporal order or spatial location are presented, would be considered as CE (Vakil et al., 1998).

In a series of studies with a variety of paradigms, it was found that while the implicit memory of context was preserved (i.e., CE), the explicit memory of context (i.e., source memory) was impaired. Vakil et al. (1998) reported that patients following TBI showed CE to the same extent as controls, i.e., better memory under consistent than varied temporal order and spatial location. However, their source memory for temporal order and spatial location was impaired. Similar findings were found with patients with TBI when the modality of presentation was used as context (Vakil et al., 1997) or when a perceptual context was used (Vakil et al., 1996). Thus, the single dissociation between an explicit test of context (i.e., source memory) and an implicit test of context (i.e., CE) is validated, based on consistent findings with patients following TBI on a variety of types of context.

Visual search: *Attentive* (*controlled*) *vs. Pre-attentive* (*automatic*)

In the previous sections it was repeatedly demonstrated that performance of individuals with TBI was impaired when the task required either strategy use, cognitive effort or deeper processing. Performance was preserved when the task did not require these effortful processes and was performed more automatically or implicitly. Although the following example is not a classical memory task, it compared the performance of individuals with TBI on tasks based on automatic versus controlled processes, which are very much related to the dissociations discussed previously.

Schmitter-Edgecombe and Robertson (2015) used two versions of a visual search task when testing individuals with moderate-severe TBI. The first one was assumed to be mediated by automatic processes and the other one by controlled processes. In both tasks, participants had to search for a target stimulus among several distracting stimuli. In the pre-attentive task, the target had a distinct feature, while in the attentive task, the target lacked such a distinct feature. Thus, while performance on the former task was mediated by automatic processes (the target "pops out"), in the latter task cognitive effort was required to detect the target. The results clearly showed a definite single dissociation between the tasks. That is, patients' performance on the pre-attentive (automatic) task was intact, while performance on the attentive (controlled) task was impaired.

3. Discussion

In this focused review, we have presented studies of various memory impairments in patients who sustained TBI. The search criterion was memory studies with moderate-to-severe TBI that found within the same sample a dissociation between a different aspect of the memory process, by demonstrating that one aspect is preserved while the other is impaired following the injury. We have argued that characterization of the memory breakdown following TBI could contribute not only to the assessment and rehabilitation of this population but also to our understanding of the composition of intact memory system. These studies, although presenting a single dissociation, can still contribute to the validation of several dissociations introduced in the literature: *central executive vs. slave systems* in working memory; *Episodic vs. Semantic* memory aspects of autobiographical memory; *Acquisition vs. Retention* and *Additions vs. Omissions* aspects of learning process; *Conceptual vs. Perceptual Priming* aspects of implicit memory; *Context Effect vs. Source Memory* aspects of context memory and *pre-attentive* (*automatic*) *vs. attentive* (*controlled*) visual search.

The dissociation of a cognitive process is critical for the study of brain-behavior relationships. Teuber (1955) introduced the concept of double dissociation, claiming that a single dissociation is limited in the effort to elucidate the relationships between brain regions and cognitive functions. Nevertheless, as we argued above, despite their limitations, single dissociations can contribute to our understanding of memory processes' architecture. In most cases, these findings, initially based on single dissociations, eventually evolved and were confirmed by double dissociations and brain imaging studies. The importance of the demonstration of the dissociation between memory processes is independent of the exact brain localization of the preserved or impaired memory processes. This is just like the contribution of the various cognitive manipulations (e.g., divided attention, exposure time, and depth of processing) reported above, that contributed to our understanding of the composition of various cognitive processes, without necessarily pointing to the brain regions associated with these processes (Jacoby, 1991).

Notwithstanding the above we would like to offer a hypothesis: Most of the impaired processes found in individuals with TBI involve, at least to some degree, the frontal lobes' functions. This hypothesis would be consistent with the neuroimaging literature (described below), documenting the frequent damage sustained by the frontal lobes following TBI. Although TBI is characterized by diffuse injury, neuroimaging studies of patients suffering from TBI have reported mostly frontal lobe lesions as well as damage to the temporal lobes, involving its medial region as well (Avants et al., 2008; Bigler, 2013; Kinch & McDonald, 2001). In addition to these cortical injuries, lesions to the white matter, expressed as a diffuse axonal injury, are also common following TBI, especially in moderate-severe TBI (Hayes et al., 2016). These lesions interfere with widespread connectivity among the frontal, temporal, and parietal lobes and various subcortical structures. This is also consistent with the conclusion reached in the review paper on the effect of moderate-to-severe TBI on memory by Vakil (2005), that the pattern of memory impairment following TBI resembles that of patients with localized frontal lobe damage.

In order to test this hypothesis, we searched for neuroimaging studies that investigated the above reported processes in individuals following moderate-to-severe TBI.

Working memory—impaired central executive (Vallat-Azouvi et al., 2007)

Baddeley (2003) postulated that the dorsolateral prefrontal cortex (dlPFC) is involved in central executive processing (see also Smith & Jonides, 1997). Barbey et al. (2013) later showed that patients with localized damage to the dlPFC were impaired in their ability to manipulate (i.e., central executive function) verbal and spatial knowledge. Owen et al. (2005) conducted a meta-analysis on neuroimaging studies using the *n*-back task as a WM measure. As the authors explained, the *n*-back task "requires on-line monitoring, updating, and manipulation of remembered information", a function carried out by the central executive component of WM (Baddeley, 2003). They found that various frontal areas were primarily involved in this task (i.e., dorsolateral & ventrolateral prefrontal cortex; frontal poles). Different brain areas are involved with the slave systems: in a meta-analysis of WM research involving brain imaging, Rottschy et al. (2012) reported that verbal WM was associated with activation of the left inferior frontal gyrus (Broca's area); Fegen et al. (2015) found a similar increased activation of the inferior as well as of the middle frontal gyri, and the superior parietal lobule in an articulatory rehearsal task. Rottschy et al. (2012) also reported that visual-spatial WM was associated with activation of the premotor cortex, posterior superior frontal gyrus, and superior and inferior parietal cortex. This study also reported on the core WM network, activated in all WM tasks, and presumably reflecting the central executive component. This core WM network consists of parts of the pre-frontal cortex, intra-parietal sulcus, anterior insula, and inferior frontal gyrus. Thus, these imaging findings suggest the involvement of various areas of the frontal lobes in central executive processing. As mentioned previously, TBI frequently affects these frontal areas.

Long term memory: *Impaired episodic memory* (Knight & O'Hagan, 2009)

From an anatomical point of view, the recall of temporal and spatial context is dependent on the PFC and the hippocampus (Eichenbaum, 2017; Howard, 2017). The activity of PFC cells predicted the recall of memory that was context-dependent (Zhang et al., 2017). Semantic memory is associated mainly with activation of the anterior temporal cortex (Hodgetts et al., 2017; Santi et al., 2016; Shimokate et al., 2015). Although one could argue that perhaps a more parsimonious interpretation is that the select cognitive deficit reflects the contribution of the medial temporal lobes, where there is considerable evidence for episodic and semantic dissociations, as opposed to the frontal lobes, which are involved in name retrieval (e.g., Leveroni et al., 2000). These findings again point to the relationship of the frontal lobes, commonly injured following TBI, to memory deficits in TBI patients.

The Learning Process: *Impaired acquisition* (DeLuca et al., 2000)

Brain imaging of the acquisition process found involvement of the hippocampus and pre-frontal cortex (Kepinska et al., 2018). Successful long-term retention (one week) of word-pairs was associated with changes in the posterior parietal cortex (Wirebring et al., 2015). Once again, we see that the frontal lobes are involved in an impaired component of memory following TBI.

The Learning Process: *impaired omissions* (Blachstein et al., 1993)

We are unaware of neuroimaging studies directly comparing brain activation under these two components of verbal learning. Thus, we cannot make any claim about the brain areas associated with these processes.

Priming: *impaired Conceptual* (Vakil & Sigal, 1997)

Regarding the relationship of priming to brain anatomy, in an fMRI study, Schacter and Buckner (1998), confirmed that both conceptual priming and deep encoding are associated with activation of the frontal lobes, while perceptual priming tasks activate more posterior parts of the brain. Recently, Gong et al. (2016) established a double dissociation of conceptual versus perceptual priming by testing patients with localized brain lesions. Comparing patients with frontal lobe or occipital lobe lesions, they found that the former performed worse on conceptual priming, whereas the latter had difficulties in perceptual priming. So here too, we find that the impaired memory process (i.e., conceptual priming) following TBI is associated with frontal lobes, frequently affected by TBI.

Context Memory: *impaired Source Memory* (Vakil et al., 1998)

We are unaware of neuroimaging studies comparing brain activation directly under these two types of context memory. However, several imaging studies have confirmed the dissociation between "item memory", that activated MTL areas, versus "source memory", that activated PFC areas (Graham & Cabeza, 2001; Liang & Preston, 2017; Meusel et al., 2017). Janowsky et al. (1989) have shown that patients with localized damage to the frontal lobes were specifically impaired in source memory. Glisky et al. (1995) demonstrated a double dissociation between item and source memory by dividing a group of elderly participants into two subgroups, based on neuropsychological tests sensitive to frontal and temporal lobe functioning. The group with low temporal and high frontal functioning was impaired on item memory tests, but not on source memory tests, and the opposite was found for the group with low frontal and high temporal functioning. As in previous examples, the memory process impaired following TBI, in this case source memory, is associated with frontal lobes' functioning, which are compromised following TBI.

Visual search: *impaired attentive* (*controlled*) (Schmitter-Edgecombe & Robertson, 2015)

The authors explain their findings based on a previous electrophysiological study by Li et al. (2013). showing that pre-attentive visual search is mediated by parietal lobes, while attentive visual search is mediated by the frontal lobes. Thus, consistent with the other dissociations presented, when a process is known to involve the frontal lobe, individuals with TBI show impaired performance.

In summary, in the above section we have attempted to support the hypothesis that the various impaired memory processes reported in individuals with moderate-to-severe TBI are associated with frontal lobes functioning. This is consistent with the reports cited above indicating the vulnerability of the frontal lobes following TBI. As stated several times above, this conclusion should be taken very cautiously because of the diffuse nature of TBI. Nevertheless, the contribution of the single dissociation in patients with TBI is independent of the exact brain region associated with these particular processes.

There are many promising technological developments which are going to improve significantly the resolution of neuroimaging. These advances could enable the association of brain structures and cognitive functions even in the case of diffuse injury following TBI. Bigler's (2016) "system biology approach" is a good example of an important move towards a better association between the cognitive deficits following TBI and its neuropathology. The strategy taken by this approach is utilization of the wide range of neuroimaging methods (e.g., MRI, fMRI, PET, SPECT, MEG, EEG) in a way that matches the cognitive process being studied. Thus, in processes in which temporal resolution is critical, MEG would be used, but when spatial resolution is more critical, then fMRI would be the appropriate tool. Using these technologies, we would hopefully be able to relate a cognitive function to a neural substrate in TBI patients, despite the diffuse nature of the injury. Such studies would enable us to detect double dissociations in this population.

The characterization of memory breakdown and the identification of different memory sub-processes following TBI could offer a significant clinical contribution to assessment and rehabilitation of this population. The refinement of the memory processes impaired or preserved following TBI is also important, because it could improve the ecological validity of the memory assessment (see Vakil, 2012). This is consistent with the Boston process approach (Milberg et al., 2009) introduced above. This approach has a great influence on neuropsychological assessment. Therefore, the research introduced above, demonstrating dissociations between preserved and impaired memory processes, could be applied to assessment. In terms of rehabilitation, too, being able to isolate more precisely the impaired and preserved memory processes could direct the clinician on what to focus in cognitive training and remediation.

Finally, this focused review is on memory processes, but we think that similar reviews need to be conducted on other cognitive aspects affected by TBI such as attention (Vakil et al., 2008), language, visual processes and executive functions (Miyake et al., 2000). Such reviews would help to elucidate the impact of TBI and would contribute not only to assessment and rehabilitation of this population, but to a better understanding of the interconnections between preserved and impaired functions in various domains.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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