Look at the frontal side of life

Anterior brain pathology and everyday executive function:
Assessment approaches and treatment

Anna Emmanouel
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Anna Emmanouel
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Promotoren
prof. dr. L. Fasotti
prof. dr. R.P.C. Kessels

Manuscriptcommissie
prof. dr. J.I.M. Egger
prof. dr. R.W.H.M. Ponds (Universiteit Maastricht)
prof. dr. J.M. Spikman (Rijksuniversiteit Groningen)
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General Introduction
Executive Functions: Functional definition and the role of the frontal lobes

Executive functions refer to an umbrella term including a wide range of abilities, such as self-awareness (i.e., developing realistic expectations about the self and setting realistic goals), goal selection, planning (of steps in complex multistep tasks), initiation and generation of behaviour, updating (keeping track of the different steps of a multistep task in working memory), inhibition/suppression of inappropriate responses and the monitoring of step sequences until the completion of an intended activity (Stuss & Levin, 2002; Stuss et al., 2002; Godefroy et al., 2003; 2010; Chan et al., 2008; Burgess and Simons, 2006; Bertens, 2015; 2016). Recently, the concept of executive function (EF) has been criticized as unclear and difficult to operationalize due to an excessive number of executive subcomponents (68) identified in several relevant studies (Packwood et al., 2011). Packwood and al. (2011) highlighted this issue and used a multi perspective approach to reduce these terms by removing their semantic and psychometric overlap. Even though executive subcomponents were reduced to 18, this is still a large number of functions. Therefore, the same authors have suggested that the concept of EF needs a revision and that many of the proposed subcomponents are not functions per se but rather a number of task-specific behaviours. With respect to brain mapping, deficits in executive functions have been traditionally related to frontal lobe damage (Luria, 1966; 1973; Stuss et al, 2000; 2001; 2007; Stuss & Levine, 2002; Alvarez & Emory, 2006; Stuss, 2011). Traumatic brain injury (TBI), for example, often results in damage to the frontotemporal (anterior) brain regions and since the mid-1980s, there has been increasing evidence that TBI leads to executive dysfunctioning, despite the recurrent presence of normal performances on other neuropsychological domains, such as basic attention and many aspects of memory (Stuss and Alexander, 2000; Stuss and Levine, 2002; Stuss, 2011; Levin et al., 2014).

Theories of executive function: from unitary “central” executive control to the functional fractionation of frontal areas into multiple executive processes

Earlier experimental investigations on the role of the frontal brain regions in human cognition and behaviour have led to the construction of cognitive information processing models. These models proposed the existence of a unitary “central” executive control system primarily regulated by the frontal lobes of the brain (Luria, 1966; 1973; Baddeley, 1986; Duncan, 1986; 1996; Norman and Shallice, 1986). A representative example of these models is the Supervisory Attentional System (SAS) model, as initially proposed by Norman and Shallice (1986). According to this model (see figure 1), there are two distinct attention processes. There is automatic attentional processing, that does not require conscious control, triggered in response to familiar environmental stimuli.
On the other hand, there is a prefrontal Supervisory Attentional System responsible for the conscious/effortful control and response to unique and novel situations (in which the automatic process would fail to respond correctly).

**Figure 1** The Supervisory Attentional System (SAS) model as initially proposed by Norman and Shallice (1986).

Contrary to the theories proposing a unitary/supervisory executive control system, more recent lesion and neuroimaging studies have provided evidence for a functional fractionation of different frontal areas into discrete executive processes rather than an integral and undivided executive system (Stuss et al., 1995; Shallice & Burgess, 1996; Godefroy et al., 1999; Stuss & Levine, 2002; Royall et al., 2002; Stuss, 2006; 2011; Gilbert et al., 2007; 2010; Godefroy, 2003; 2010). Miyake et al. (2000), for example, confirmed the functional separability of three distinct executive functions, namely mental set shifting (Shifting), information updating and monitoring (Updating), and inhibition of prepotent responses (Inhibition). Furthermore, during the last three decades lesion and neuroimaging studies investigating the role of the anterior brain regions in attention and executive function have supported the fractionation of the frontal central executive system into separate putative subcomponents, by consistently finding three distinct types of executive functions related to different frontal cortical-subcortical neural circuits (for a review see Stuss & Alexander, 2007; Petrides & Pandya, 2007; Gilbert et al., 2010; Stuss, 2011).

At a behavioural level, an additional recognition of the fractionation of the executive system into multiple processes has been recently found by Simblett and Bateman (2011), who examined the results of 363 TBI patients on the Dysexecutive Questionnaire.
(DEX) with a Rasch analysis. This analysis resulted in several new subscales, suggesting different executive dimensions rather than a single construct (Stuss, 2011).

Figures 2 and 3 illustrate an example of three separate neural circuits underlying the functional fractionation of the frontal lobes.

<table>
<thead>
<tr>
<th>Frontal Structures/ Circuits for Broad Executive Functions</th>
<th>Description</th>
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<tr>
<td>Dorsolateral prefrontal circuit</td>
<td>Managing functions: holding, manipulating, planning, executing, organizing and shifting</td>
</tr>
<tr>
<td>Orbital prefrontal circuit</td>
<td>Regulation of emotions and behaviours: initiating, timing, sustaining, modulating, and inhibiting</td>
</tr>
<tr>
<td>Anterior cingulate circuitry</td>
<td>Monitoring, gauging, inhibiting and shifting</td>
</tr>
</tbody>
</table>

**Figure 2** Functional differentiation of three frontal lobe circuits into three broad types of executive functions (Stuss, 2011).

**Figure 3** Figure illustrating the frontal cortical–basal ganglia–thalamic circuits, underlying the fractionation of the frontal functional regions. Adopted from Stuss (2011, pp. 762). Copyright E INS. Published by Cambridge University Press, 2011.
Assessment of executive functions: Critical issues

A. Do traditional executive tests provide evidence of functional/neuroanatomical relationships between types of executive dysfunction and anterior brain damage?

In clinical practice, deficits in particular executive domains were detected in brain-injured patients with distinct types of injury using different executive tasks. These tasks were initially developed to discriminate anterior from non-anterior pathology (for a review see Alvarez and Emory, 2006). Over the last forty years the validity of these tasks to accurately identify disorders due to anterior damage were repeatedly investigated. Moreover, these tasks were used in both clinical assessment and research and found to be valid measures of anterior executive dysfunction (Levine and Stuss, 2002; Alvarez and Emory, 2006). Examples of these commonly used executive tests include: i) the Wisconsin Card Sorting Test (WCST; Milner, 1963; Heaton, 1981; 1993), ii) the Tower of London test (Shallice, 1982), iii) the Verbal Fluency Task (VF; Lezak, 1995; Spreen and Strauss, 1998), iv) the Stroop Test (Stroop, 1935; Golden, 1978; Lezak, 1995), and v) the Trail Making Test (Reitan, 1958; Lezak, 1995; Levine and Stuss, 2002; Alvarez and Emory, 2006).

Above all, several studies (including neuropsychological, lesion and neuroimaging investigations) have established links between the performance on these tasks and the primary involvement of the frontal lobes (Robinson et al., 1980; Eslinger & Grattan, 1993; Lezak, 1995; Spreen & Strauss, 1998; Stuss et al.; 1998; Miyake et al., 2000; Stuss & Alexander, 2000; Stuss & Levine, 2002; Stuss et al.; 2000; 2001; 2005; 2011; Royall et al., 2002; Henry and Crawford, 2004a; 2004b; Alexander et al., 2005; 2007; Picton et al., 2006; 2007). These studies concluded that traditional executive tests are multifactorial and demand various executive processes, such as overcoming the tendency to enact strong stimulus–response associations that are currently not relevant (inhibition), maintaining correct responses fitting to a particular sorting principle and avoiding perseverations (by effectively incorporating feedback), holding and manipulating information over delay periods, especially in the face of interference (working memory), switching and set shifting (flexibility), self-initiation (because there is an absence of external cues to prompt behaviour), strategy application and/or monitoring of behavioural sequences over long periods of time (multitasking or prospective memory) (Gilbert and Burgess, 2008).

However, the appropriateness of these standard neuropsychological tests to identify executive deficits in patients with frontal lobe lesions, for instance in patients with TBI, has been recently questioned in other lesion and functional neuroimaging studies (for a review see Alvarez and Emory, 2006; Chan et al., 2008; Sbordone, 2010; Stuss, 2011). Although primarily associated with focal frontal lobe damage, deficits in standard executive tests have been shown to occur in a large number of
other clinical conditions affecting the interconnections of frontal lobes with posterior and other subcortical non-frontal brain regions through axonal or white matter changes, such as in diffuse traumatic brain injury (Levine et al., 1998), multiple sclerosis (McDonald and Ron, 1999), ischemic white matter disease (Swartz et al., 2008), aging (Raz, 1998), dementias (Neary et al., 1998), psychiatric conditions (Cohen and Servan-Schreiber, 1992; Mayberg, 1997), Parkinson’s disease (Askin-Edgar, 2004), Huntington’s disease (Jankovic and De Leon 2003) and Korsakoff’s syndrome (Lezak, 1995; Barch and Buckner 2003). Recent lesion and neuroimaging researches have also provided evidence of executive impairments in experimental and traditional executive tests after TBI due to a disconnection of the frontal lobes from subcortical or posterior regions or due to damage to the subcortical white matter, the basal ganglia and the thalamus (Anderson et al, 2010; Peterson et al., 1999; D’Esposito et al., 2000; Elliot, 2003; Godefroy et al., 2003; Carey et al., 2008; Niogi et al., 2008; Little et al., 2010; Kinnunen et al., 2011). This implies that a wider network of brain areas is involved in performing well on these standard executive tests (Stuss et al., 1995; Peterson et al., 1999; D’Esposito et al., 2000; Stuss & Alexander, 2000; Royall et al., 2002; Stuss & Levine, 2002; Heyder et al., 2004; Alvarez & Emory, 2006; Collete et al., 2006). However, a greater specificity has yet to be found with respect to the role of these subcortical pathologies in the impaired performance on standard executive tasks.

Beyond their executive demands, traditional executive tests may also require abilities dependent on non-frontal areas. For example, it has been repeatedly suggested that posterior regions may play a role in the content-specific sensory, perceptual, memory and comprehension aspects of these multi-component executive tests rather than in their ‘central’ executive characteristics (Carter et al., 1995; Nagahama et al., 1996; Ragland et al., 1998; Brown et al., 1999; Peterson et al., 1999; Rogers, 2000; Royall et al., 2002; Stuss and Levine, 2002). Within this framework, traditional executive tests may be insufficient to provide clear-cut correlations between impairments in executive processes and anterior lesions, even though they were designed to evaluate damage to the frontal lobes of the brain (Sbordone, 2010). Consequently, this hampers the accurate assessment and corresponding treatment of executive problems following TBI (Sohlberg and Matter, 2001; Levine et al., 2011). Beside this, an additional difficulty in utilizing standard executive tests for the assessment of executive functioning lies in the apparent fractionation of the executive processes. For example, a patient’s performance on one executive test may have little or no predictive value for how he or she may perform on another test (Burgess, 1998; 2010; Chan et al., 2008).
B. Do traditional executive tests assess real-life executive problems in patients with frontal lobe injury?

Another important critical issue is that the majority of the conventional executive tests have been criticized with respect to their lack of ecological validity, i.e. their inability to assess the executive problems of patients with moderate to severe frontal lobe damage (e.g., moderate to severe TBI) in real-life settings (Sbordone, 2000; 2010). This criticism is based on the fact that patients with moderate to severe TBI have often been found to perform equally well as healthy controls on traditional executive tests when these were administered in a controlled, quiet, and highly structured setting within the neuropsychologist’s office (Sbordone 1996, 1997; Burgess et al., 1998; 2006). However, when the same patients were observed in ill-structured or complex real-world settings (e.g. their home or the shopping mall), they had executive difficulties alongside with neurobehavioral dysexecutive symptoms (Shallice & Burgess, 1991; Burgess et al., 1998; Sbordone, 2010). This discrepancy between standard and real-life executive tasks implies that the data derived from conventional tests may not reflect the executive difficulties of patients with TBI in complex activities of daily living (Wilson et al., 1996; 1998; Burgess et al., 1998; Chan et al., 2008; Stuss, 2011).

Consequently, everyday executive problems of patients with moderate or severe TBI are difficult to examine with standard neuropsychological tests (O’Shanick and O’Shanick 1994). Bechara et al. (1994) have emphasized that, if the tests that are administered do not rely on demands of everyday life, they will most likely fail to detect deficits in daily executive functioning. Therefore, it remains unclear whether traditional executive tests can predict how patients with TBI will function in everyday or real-world settings that are often complex, noisy, ill-structured, and at times even chaotic (Sbordone, 2000; 2010). By using only conventional executive tasks, a neuropsychologist may miss important information about the daily functional difficulties of these patients and not be aware of their problems if he/she has not observed patients’ performance in real-life tasks or has never interviewed the significant others of these patients. Chaytor and Schmitter-Edgecombe (2003) and Chaytor et al. (2006) compared the neuropsychological test scores of patients with brain injuries on measures of everyday and real-world functioning. They found that the neuropsychological test scores of these patients were often either unrelated or poorly related to measures of everyday functioning and their behaviour in real-world settings (Sbordone, 2010). So, these tasks seem unable to capture the real functional status of a patient, as manifested in terms of his/ her executive dysfunctions in everyday life (Chan et al., 2008).
C. The need for ecologically valid tests for the assessment of executive function

The last three decades there has been an increasing emphasis on the development of newer, more open-ended and ecologically valid tests and batteries for the clinical assessment of deficits in various executive domains after brain damage. Many of these newer tests also include everyday life questionnaires to capture subjective dysexecutive complaints (Wilson et al., 1996; Gold et al., 1997; Robertson et al., 1997; Burgess et al., 1998; Grace, et al., 1999; Chan, 2001; for a review see Chan et al., 2008). These tests have been specifically designed to assess the severity of functional difficulties in executive functioning. The scores on these tests should predict the performance of brain-injured patients in real-life activities. They should also contribute to a better planning and implementation of rehabilitation programmes. A representative example of ecologically valid tests is the Behavioural Assessment of the Dysexecutive Syndrome (BADS; Wilson et al., 1996, see figure 4).

Figure 4  An example of Ecologically valid executive tests: Behavioural Assessment of the Dysexecutive Syndrome (BADS; Wilson et al., 1996).
The BADS is a multifaceted battery consisting of several executive subtests that resemble real-life situations. These subtests evaluate a variety of executive processes such as shifting, action planning, strategy formation, problem-solving, compliance with rules and instructions, task and time scheduling and monitoring. The BADS also includes a 20-item questionnaire, the Dysexecutive Questionnaire (DEX) that evaluates patients' daily dysexecutive symptoms and neurobehavioural changes. This questionnaire may be completed by the patient and/or by a significant other. The BADS has been found to be a better predictor of a patient’s executive functions in real-world situations than the Wisconsin Card Sorting Test (Wilson et al. 1996). However, the superiority of the BADS compared with other executive tests in predicting executive competency in daily life has been challenged by more recent studies (Norris and Tate, 2000; Manchester, et al., 2004; Boelen et al., 2009). With respect to the construct validity of the BADS, only its ability to discriminate patients with brain damage or other clinical conditions from healthy controls has been consistently confirmed (Evans et al., 1997; Wilson, 1996; 1998; Burgess et al., 1998; Krabbendam et al., 1999; Ihara and Berrios, 2000; Norris and Tate, 2000; Cavanagh et al., 2002; Chan, Chen et al., 2004; Heyder et al., 2004; Boelen et al., 2009; Vargas et al., 2009). However, despite the fact that frontal lobe damage potentially causes moderate to severe daily executive problems, little is known about the validity of the BADS to detect pure executive difficulties related to anterior brain pathology (Chamberlain, 2003).

‘Script generation’ is another example of free-response, real-life executive task shown to be mainly affected in patients with TBI (Allain et al., 2011; 2012; Boelen, 2011). According to Wood and Grafman (2003), scripts are stored cognitive schemas of familiar everyday scenarios consisting of sequences of events/actions that are activated when real-world situations demand their planning and generation. Thus, difficulties in these tasks may reveal specific executive deficits in action planning and completion of multistep activities of daily living, providing useful indices for the assessment and treatment of impairments in serial-order and goal-directed behaviour after TBI (Allain et al., 2011; Boelen et al., 2011).

**D. Ecologically valid executive tests and evidence for everyday executive dysfunction and relation to anterior brain damage.**

**Contributions to clinical practice**

So far it has been consistently shown that patients with predominant frontal lobe damage (as is the case after TBI) may perform well on standard executive tests but still face profound difficulties in real-life, with devastating consequences on functional independence and overall quality of life (Wilson et al., 1996; Burgess et al., 1998; Fasotti and Spikman, 2002; Spikman et al., 2010; Sbordone, 2000; 2010). The impact of frontal lesions on standard executive tests has been extensively investigated.
These tests were generally found to be inadequate to detect executive difficulties after anterior brain damage. This may be due to the structured nature of these tests and the fact that anterior brain lesions mainly affect executive performance in ‘open-ended’ real-world conditions (Sbordone, 2000; 2010). However, despite prominent problems in everyday executive tasks after TBI, the effects of anterior lesions on ecologically valid tasks (for instance the BADS) and questionnaires of daily executive functioning (e.g. the DEX), have been rarely examined. This might be due to their functional orientation. These tasks were developed to detect executive deficits in complex activities of daily living (Wilson, 1996; 1998; Burgess et al., 1998; Chan et al., 2008; Sbordone, 2000; 2010).

Another problem of several investigations is the heterogeneity of the participant patient groups. (Wilson et al, 1996; Prigatano et al., 1996; Burgess et al., 1998; Evans et al., 1997; Sbordone et al., 1998; Norris and Tate, 2000; Boelen et al., 2009). Only Channon and Crawford (1999) used a lesion location criterion to investigate the effect of anterior and posterior lesions on a set of ecologically valid problem solving tests, including the BADS battery (Channon and Crawford, 1999; Channon, 2004). No significant effects of lesion location (neither anterior nor posterior) were found for any of the BADS subtests. However, this study was hampered by the modest sample sizes of patients with anterior and posterior lesions (N=16 and N=9 respectively). Only the Six Element Test, part of the BADS, has been repeatedly shown to be valid and sensitive with reference to patients with frontal lobe lesions and other patients with neurological and psychiatric disorders with evident frontal lobe pathology (Burgess et al., 1998; Chan & Manly, 2002; Chan et al., 2003; Chan, Chen, et al., 2004; Chan, Chen, Cheung, et al., 2006; Chan, Chen, & Law, 2006; Burgess et al., 2006; Chan et al., 2008).

Nevertheless, additional research is needed to elucidate the functional/anatomical relationship between ecologically valid executive tasks and anterior brain dysfunction. The results could provide useful indices of the specific everyday executive impairments of patients with TBI and, thus, guide the development and application of more appropriate approaches in both the clinical assessment and cognitive treatment of impairments in real-life.

**Rehabilitation of Executive dysfunctions: Critical issues**

Deficits in the selection and execution of cognitive plans, their updating and monitoring, the inhibition of irrelevant responses and problems with goal-directed behaviour usually result in disorganized behaviour, impulsivity and problems in goal management and self-regulation (Levine et al., 2011; Spikman et al., 2010). These deficits appear to be the most prominent executive problems in the everyday life of patients with brain injuries, especially when performing multistep activities of daily living (Mateer et al., 1987; Robertson, 1996; Levine et al., 2000; Sohlberg & Turkstra,
The high prevalence of such deficits in brain-damaged patients and their severe functional impairments in all domains of life represent a major challenge for rehabilitation and underlie the need for developing effective interventions (Levine et al., 2000; Hart and Evans, 2006; Bertens et al., 2013). However, in a recent review of 55 studies on rehabilitation of executive dysfunction (Levine et al., 2011), only 16% met criteria for evidence sufficient to guide treatment (Cicerone et al., 2000, 2005; Rohling et al., 2009; Levine et al., 2011). Research in the area of rehabilitation of executive impairments is limited by the heterogeneity of patient samples, the lack of control groups, the absence of theoretically based intervention protocols, unspecified criteria for the generalization of the effectiveness of the treatment and limited outcome assessment (Levine et al., 2011).

A critical issue in rehabilitation is whether interventions should be aimed at treating the underlying impairment (i.e. retraining/ restoring the impaired function) or at providing brain-injured patients with strategies that enable them to compensate for the impairment (compensatory approach). A list of the approaches applied so far for the management of difficulties in executive functions, alongside with supportive empirical evidence, is presented in Table 1. The evidence that executive problems can be restored is not wholly convincing, whereas there is more evidence that self-instructional compensatory strategies can produce real benefits (Evans, 2003; Sohlberg and Torstar, 2011). With respect to the self-instructional approach, the patient is trained in using mental check lists and self-instructions while executing multistep tasks. The main treatment goal is to help patients slowdown their approach to the task and effectively develop a habit of exerting more cognitive control rather than responding impulsively (Evans, 2003; Sohlberg and Matter, 2001; Sohlberg and Turkstra, 2011).

Within this framework, Fasotti et al. (2000) developed a compensatory strategy training called Time Pressure Management. The aim was to teach brain-injured patients a technique to help compensate for slow information processing. The strategy consisted of a general self-instruction followed by four specific steps. The authors showed that use of the strategy helped patients improve their performance on a practice task and the treatment effects did generalize to other measures of speed and memory function.

Another well-studied self-instruction intervention is Goal Management Training (GMT), which relies on theories of goal processing and sustained attention (Duncan’s goal neglect theory; Duncan, 1986; Duncan & Owen, 2000; Duncan et al., 2000). In his influential goal-neglect theory, Duncan argues that human behaviour is goal-oriented or goal-directed and controlled by a list of goals or subgoals. These goals are formulated, stored and checked in order to behave optimally in response to environmental or internal demands. One of the main functions of these goals is to impose a structure on behaviour by controlling the activation or inhibition of behaviour.
**Table 1** Summary of treatment approaches in rehabilitation of executive functions

<table>
<thead>
<tr>
<th>Metacognitive strategy</th>
<th>Description</th>
<th>Supporting research evidence</th>
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<tr>
<td>Time Pressure Management (TPM)</td>
<td>Problem-Solving process: Intervention first helps with increasing self-awareness and acceptance of disability, then participants taught step-by-step problem-solving approach rehearsed under increasing distractors.</td>
<td>Fasotti et al. (2000)*.</td>
</tr>
<tr>
<td>Problem Solving with impulsivity control</td>
<td>Problem-Solving process: Participants taught to observe and record impulsive reactions to problem-solving situations and identify strategies to facilitate organised behaviours.</td>
<td>Rath, Simon, Langenbahn, Sherr, &amp; Diller (2003)*.</td>
</tr>
<tr>
<td>Verbal Mediation</td>
<td>Self-Instruction process for problem-solving and goal completion: Participants taught to verbalize steps of multistep activities and fade talking to whispering and then to inner speech.</td>
<td>Cicerone and Wood (1987); Cicerone and Giacino (1992).</td>
</tr>
<tr>
<td>Goal Attainment</td>
<td>Goal-setting process: Participants taught steps to set goals and actively monitor progress towards goals.</td>
<td>Webb and Gluecauf (1994).</td>
</tr>
<tr>
<td>Goal Management Training (GMT)</td>
<td>Goal-completion process: Participants taught six steps: Stop, define main task, list steps, learn steps, execute task, check results.</td>
<td>Levine et al. (2000)*.</td>
</tr>
<tr>
<td>Self-Monitoring (WSTC)</td>
<td>Self-Monitoring process: Participants taught self-monitoring steps associated with the acronym WSTC: <strong>What am I supposed to be doing?</strong> <strong>Select a strategy;</strong> <strong>Try the strategy;</strong> <strong>Check the strategy.</strong></td>
<td>Lawson and Rice (1989).</td>
</tr>
<tr>
<td>Self-Monitoring (Error self-regulation)</td>
<td>Self-Monitoring process: Participants taught to evaluate previous performances, anticipate future difficulties, and consider possible corrective strategies. Predictions were compered to therapists’ evaluations.</td>
<td>Ownsworth, Quinn, Fleming, Kendall, and Shum (2010).</td>
</tr>
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* indicates that research provided a high level of supporting evidence using a randomized controlled trial.
that facilitates or prevents task completion. The behaviour of patients with frontal lobe damage is usually disorganized and fails to achieve intended goals, revealing the involvement of the frontal lobe in goal-oriented or goal-directed behaviour. These patients tend to lose sight of their goals, a phenomenon characterized by Duncan as goal neglect, and their actions may become random or stuck on one or more subgoals (Chan et al., 2008).

**Goal Management Training: Description, aims and effectiveness**

In order to address these difficulties Robertson (1996) have developed Goal Management Training (GMT). GMT is focused on helping patients with partitioning a main goal into discrete sub-goals. Subsequently, they learn a mental list of these subgoals that enables them to maintain focus in multistep tasks. Specifically, during GMT, patients with brain injuries are trained in learning and applying an algorithm (Bertens et al., 2013; 2015) consisting of six stages (see figure 5). These stages characterize the most crucial elements for maintaining goals in mind. The six stages are:

1. **STOP** for letting patients asking themselves what they are doing at the moment;
2. **DEFINE** for defining the main task out of a set of irrelevant or less prioritized tasks;
3. **LIST**: Each main task is analysed and listed as a sequence of discrete steps to-be-learned for the accomplishment of the chosen or the most prioritized task;
4. **LEARN** for asking them whether they know the planned steps in order to initiate the chosen or prioritized task;
5. **DO IT** by executing the task; and
6. **CHECK** for monitoring the on-going task.

Levine et al. (2000) have shown the clinical utility and training efficacy of GMT in a group patient with frontal lobe lesions. However, these authors also mentioned that the success of GMT depended on a number of factors, including self-awareness and motivation to complete the training programme. GMT has received empirical support in studies of patients with traumatic brain injury (Levine et al., 2000b; Fish et al., 2007) and normal aging (Levine et al., 2007; van Hooren et al., 2007). Case studies investigating GMT in patients with focal cerebral damage (Schweizer et al., 2008) and encephalitis (Levine et al., 2000b) have also been performed. All these studies have shown positive effects and generalization of GMT to real-life activities such as financial management (Grant et al., 2012) and meal preparation (Levine et al., 2000b). Recent randomized controlled trials indicate that a combination of GMT with other training methods, either as part of a multifaceted rehabilitation program (Spikman et al., 2010) or by incorporating errorless learning in GMT, may further increase the effectiveness of GMT on everyday task performance in individuals with brain injury. Bertens et al. (2015), for example, showed that brain-injured patients who were
administered the combined treatment of GMT and errorless learning improved to a larger extent in everyday task performance than participants who only received conventional GMT, in the absence of any baseline differences. Apparently, in addition to the regulation of behaviour, the effectiveness of GMT may require its combination with other training techniques.

Figure 5 GMT algorithm adapted from Levine’s 2000 figure (Bertens et al., 2013).
Incorporating an updating working memory strategy in GMT: A new approach for the treatment of disorganised behaviour after acquired brain damage

Working memory (WM) is a fundamental cognitive mechanism and crucial to complex everyday functioning (Dujardin et al., 2004, Dahlin et al., 2008). WM is necessary for staying focused on a task, blocking out distractions, keeping oneself updated and aware of what is going on during this process until the completion of a task (Salminen, et al., 2012; Smith, 2013). WM impairments result in loss of sustained attention or in memory problems, such as forgetting what to do in the few seconds of walking from one room to the other, or being easily distracted while trying to focus on a task and not being able to accomplish an activity according to a plan (Smith, 2013).

According to Miyake et al.’s model of executive functioning (2000), the updating component of WM is one of the three major executive factors (along with shifting and inhibition) responsible for keeping track of action sequences necessary for the execution of multiple tasks (Miyake et al., 2000; Smith & Jonides, 1999). Updating has also been characterized as one of the most important executive functions in everyday life (Channon et al., 2004; Collette & Van der Linden, 2002, Dahlin et al., 2008; Klingberg, 2010). Updating helps us actively maintain step sequences in mind while using this information to execute an intended complex task (purposive/goal-directed behaviour). Updating and cognitive control seem to be especially impaired in patients with executive deficits after TBI (Miller & Cohen, 2001). Patients with TBI usually exhibit poor updating capacities and face a lot of difficulties in encoding and learning lists of steps needed for the completion of multistep real-life tasks. These tasks require continuous updating of WM storage with new incoming information (new steps to-be-learned) while retaining these new steps in sequence with previously learned steps, until the successful accomplishment of the task (Dahlin et al., 2008; Sohlberg and Turkstra, 2011). Consequently, difficulties in goal-directed behaviour combined with working memory problems may together impede the correct execution of multistep everyday tasks. Thus, the incorporation of an updating strategy in GMT may further facilitate learning and mental maintenance of step (subgoal) sequences in an on-going multistep activity of daily living (Desjardin et al., 2004, Dahlia et al., 2008; Nett et al., 2010; Smith, 2013; Truedsson & Strohmayer, 2013).
Outline of this thesis

This thesis consists of two parts. The first part includes three chapters and tries to shed light on the functional/ anatomical relationship between real-life executive difficulties and anterior brain pathology. As mentioned before, patients with moderate or severe TBI (mainly affecting the frontal regions of the brain) may perform (at least to some extent) well on standard executive tests, while still encountering severe executive difficulties in real-life executive tasks as well as exhibiting moderate to severe behavioural dysexecutive symptoms. This part of the thesis is aimed at further exploring the effects of anterior lesions on ecologically valid tasks, since little is known in this area of research. Such studies may contribute to a better understanding of specific executive dysfunctions and symptoms related to anterior damage and, thus, adequately guide clinical assessment and treatment of everyday executive deficits of brain-injured patients.

The first chapter of the first part (chapter 2) describes a lesion study that investigates the validity of the BADS to detect real-life executive problems related to anterior brain damage. Previous studies had investigated the validity of the BADS to distinguish healthy controls from brain damaged patients without specific lesion location criterion. In this study we compared the performances of 30 patients with anterior lesions on all the BADS executive subtests (and additional standard tests) to those of 22 patients with posterior lesions, all signalled by their therapists for having executive problems in everyday functioning. The performances of both patient groups were also compared to those of a group of healthy adults. Our aim was to examine the validity of the BADS to discriminate anterior from posterior lesions and search for BADS test scores (and standard executive tests performances) that could be used as sensitive and specific indicators of everyday executive dysfunctions related to anterior pathology. The findings of this study could provide useful information for a more accurate assessment and management of executive problems of patients with TBI in real-world complex situations.

In chapter 3 we investigate the validity of the DEX-questionnaire to reliably identify the impact of anterior lesions on behavioural changes as observed in real-life by the patients themselves (DEX-self) and their therapists (DEX-TH). This lesion study included the two patient groups who participated in the previous study (anterior vs. posterior) and the therapists of both groups. Our main goal was to explore the validity of the DEX-Questionnaire at identifying differences in the severity of dysexecutive symptoms according to lesion location. We also examined the strength of associations of the DEX-Self and the DEX-TH reports with the sub-tests of the BADS as well as two other real-life executive tasks, the Everyday Description Task (EDT) and the Twenty Question Test (TQT). Based on the findings of a previous study conducted by Bennett and al. (2005), we expected that the DEX-TH reportings would better evaluate the
severity of dysexecutive symptoms in both patient groups, with more severe changes reported for the anteriorly lesioned group.

Chapter 4 is another lesion study aimed at investigating difficulties in script generation linked to anterior lesions. For this purpose, we compared the performances of the aforementioned 30 patients with anterior lesions to those of the 22 patients with posterior lesions on eight scripts derived from the EDT. All patients exhibited everyday executive problems and were also compared to a group of healthy controls. Several indices of the EDT were investigated. Moreover, we explored whether script generation can be predicted by specific executive processes.

The second part of this thesis is devoted to a recently developed treatment approach that incorporates the updating of working memory in stage four (learning the list of steps) of GMT. In particular chapter 5 describes the rationale and the training protocol of this new combined treatment. Problems such as losing track of the steps in an on-going multistep everyday activity or having difficulties in staying focused on a sequence of subgoals/steps are examples of working memory problems in brain-injured patients that impede learning and achieving subgoals in GMT (Dujardin et al., 2004; Dahlin et al., 2008; Netto et al., 2010; Smith, 2013; Truedsson & Strohmayer, 2013). Hence, difficulties in goal-directed behaviour combined with working memory problems may prevent the correct accomplishment of multistep everyday tasks. Therefore, the updating strategy is targeted at facilitating the learning and maintenance of the step sequencing at stage 4 of GMT. The acquisition of these steps in stage 4 is necessary for the completion of complex real-life tasks.

Chapter 6 describes a randomized controlled study investigating the efficacy of the new combined (experimental) treatment of GMT and Updating of Working Memory Technique (GMT+WMT) compared to a control working memory training (WMT) designed for other purposes. Eighteen brain-injured patients in the chronic stage were randomly assigned either to the experimental GMT+WMT or the control WMT treatment condition. Pre-treatment and post-treatment comparisons in each of these primary tasks and in several secondary and ‘additional’ neuropsychological measures were performed.

Finally, in chapter 7, a summary and discussion of all the empirical chapters is presented. The clinical implications and possible limitations of the findings are discussed and directions for future research are provided.
References


CHAPTER 1


Sensitivity, specificity and predictive value of the BADS to anterior executive dysfunction

Published as:
Abstract

In this study we investigated the validity of the BADS subtests to adequately discriminate anterior lesions (AL) from posterior lesions (PL). Therefore, we compared the performances of 30 patients with AL, 22 patients with PL and 29 healthy controls (HC) on the BADS subtests. Seven standard executive test variables were also examined. Our multiple comparisons showed that the BADS Zoo Map–Part 1 was not indicative for AL, whereas Rule Shifting, Action Program, Key Search, Zoo Map–total score, and BADS–total score were found to be sensitive to AL. Importantly, the Modified Six Element Test (MSET), and the Zoo Map–Part 2 were highly specific for AL. In both BADS subtests patients with AL performed significantly worse than either the PL or the HC groups, whereas no significant differences on the same variables were found between PL and HC individuals. Further logistic regression analysis revealed that the BADSMSET was the best predictor for distinguishing patients with AL from those with PL, correctly classifying 78.8% of the patients. These results suggest that the BADSMSET is an accurate screening tool for the detection of anterior pathology. Poor performance on this BADS subtest is a significant indicator of executive dysfunctioning after anterior brain damage.

Keywords: Neuropsychological assessment; Executive functioning; Ecological validity; Brain injury; Frontal lobes.
Introduction

Executive functions generally encompass a set of higher-order cognitive processes (e.g., planning, strategy implementation, initiation, sequencing, monitoring, problem-solving and abstract reasoning, selective attention and inhibition, working memory, rule deduction, cognitive flexibility and set shifting), responsible for the control and regulation of content-specific cognitive processes and for the effective completion of complex goal-directed, future-oriented behaviour (Norman & Shallice, 1986; Burgess, 2000; Stuss & Levine, 2002; Royall et al., 2002; Andres, 2003; Godefroy, 2003; Alvarez & Emory, 2006). A large number of lesion studies have found evidence for a relation between executive dysfunction and damage to the anterior areas of the brain. Patients with anterior lesions, for example, were found to perform worse than patients with non-anterior lesions on tests commonly used to measure executive dysfunction, such as the Wisconsin Card Sorting Test (WCST), Verbal Fluency (VF), the Stroop Word Colour Test (SWCT) and the Trail Making Test (TMT) part B (Milner, 1963; Spreen & Strauss, 1998; Stuss et al.; 1998; Troyer, 1998; Arbuthnott & Frank, 2000; Stuss et al, 2000; Stuss & Alexander, 2000; Stuss et al.; 2001; Greve et al., 2002; Stuss & Levine, 2002; Royall et al., 2002; Heyder et al., 2004; Alvarez & Emory, 2006). Nevertheless, the sensitivity and specificity of these four standard executive tests to adequately detect anterior lesions has recently been challenged (Barcelo, 2001; Barcelo & Knight, 2002; Alvarez & Emory, 2006).

According to Alvarez and Emory’s meta-analytic review (2006), sensitivity and specificity indicate the accuracy with which an executive task distinguishes anterior from non-anterior lesions. In other words “… persons with any other type of brain damage (any other than anterior damage) would have to perform as well as healthy controls, and persons with frontal lobe lesions would have to perform significantly worse than all other brain-damaged groups on this task” (Alvarez & Emory, 2006, p. 23). However, several studies showed almost normal performance of patients with anterior lesions on these standard executive measures (Eslinger & Damasio, 1985; Heck & Brayer, 1986; Shallice & Burgess, 1991; Ahola et al., 1996; Alvarez & Emory, 2006), whereas other studies found that patients with posterior or non-anterior cortical damage also exhibit poor performance on these tests (Crockett et al., 1986; Anderson et al., 1991; Elliot, 2003; Godefroy, 2003; Alvarez & Emory, 2006). These findings are in agreement with functional neuroimaging studies, showing a wider network of both anterior and posterior areas being activated when healthy people are engaged in standard executive tests (Stuss et al., 1995; Peterson et al., 1999; D’esposito et al., 2000; Stuss & Alexander, 2000; Royall et al., 2002; Stuss & Levine, 2002; Heyder et al., 2004; Alvarez & Emory, 2006; Collet et al., 2006). It has been suggested that posterior regions are responsible for the sensory, perceptual, memory and comprehension aspects of these tasks, but not necessarily for their specific executive
characteristics (Carter et al., 1995; Taylor et al., 1997; Nagahama et al., 1998; Ragland et al., 1998; Brown et al., 1999; Peterson et al., 1999; Rogers, 2000; Royall et al., 2002; Stuss & Levine, 2002; Alvarez & Emory, 2006).

Although a vast number of lesion and neuroimaging studies have investigated the neuroanatomical sensitivity and the specificity of standard executive tests for anterior lesions (see Alvarez & Emory, 2006), the validity of more ecologically valid executive tests in relation to anterior brain pathology has been less often studied (Shallice & Burgess, 1991; 1993; Levine et al., 1998; Burgess, 2000b; Goel & Grafman, 2000). Ecologically valid tasks are designed to be more predictive of real-life performance, which standard executive tests often do not. Examples of ecological valid tests are the Multiple Errands Test (Shallice & Burgess, 1991) and the Behavioural Assessment of Dysexecutive Syndrome (BADS, Wilson et al., 1996).

There is a relative dearth of studies that have examined the sensitivity and the specificity of the BADS in relation to lesion location. The majority of studies have included unselected brain impaired patients and healthy participants as controls. (Wilson et al., 1996; Prigatano et al., 1996; Burgess et al., 1998; Evans et al., 1997; Sbordone et al., 1998; Norris and Tate, 2000). Wilson et al. (1996) administered the BADS in a group of brain-injured patients that included patients with traumatic brain injury, dementia, stroke or tumours, and in healthy controls. This study showed that brain-injured patients performed worse on all subtests of the BADS than the control group (Wilson, 1996; 1998). The construct validity of the BADS and its sensitivity to cerebral dysfunction was also confirmed by other lesion studies (Norris and Tate, 2000; Boelen et al., 2009). These studies show that the BADS adequately discriminates brain-injured patients from healthy controls.

Furthermore, a limited number of group studies have attempted to investigate the sensitivity of the BADS with brain-injured and psychiatric populations exhibiting executive deficits functionally related to anterior brain pathology (Evans et al., 1997; Burgess, Alderman, Emslie, Evans, & Wilson, 1998; Burgess, Veitch, de Lacy Costello, & Shallice, 2000; Burgess et al., 2006; Krabbendam et al., 1999; Ihara & Berrios, 2000; Cavanagh et al., 2002; Chan & Manly, 2002; Chan, Hoosain, Lee, Fan, & Fong, 2003; Chan, Chen, Cheung, & Cheung, 2004; Chan, Chen, Cheung, Chen, & Cheung, 2006; Chan, Shum Toulopoulou, & Chen, 2008; Vargas et al., 2009). Only one subtest, the Six Element Test (SET, Shallice & Burgess, 1991; Burgess et al, 1996b; 2000b) has been shown to be sensitive to neurological and psychiatric conditions functionally related to anterior damage (Burgess et al., 1998; 2006; Chan et al., 2003; 2004; 2006; Chan, Chen, & Law, 2006; 2008; Burgess et al., 2006). However, the conclusions drawn from these studies were limited, due to the heterogeneity of the selected patient groups and the lack of reference groups with lesions elsewhere in the brain. Channon and Crawford (1999) used the lesion location criterion in order to investigate the sensitivity and the specificity of the BADS and
other real-life executive tasks (see also Channon, 2004). No significant effects of lesion location (anterior nor posterior) were found for any of the BADS subtests. However, this study was hampered by a modest sample size of anterior and posterior patients (N=16 and N=9 respectively).

The first purpose of the present study was to investigate the impact of lesion location on the performance of patients with everyday dysexecutive symptoms in ecologically valid executive tasks such as the BADS. Our aim was to examine the sensitivity and the specificity of the BADS subtests with regard to anterior and posterior brain damage. Therefore, we recruited anteriorly and posteriorly brain-injured patients, based on reports and observations of these patients’ dysexecutive behaviour in everyday life. The inclusion criteria in this study were lesion location and deficits in daily life executive function as reported by external raters (patients’ therapists). Thus, we focused on a sample of brain-injured subjects with observable dysexecutive symptoms, to investigate whether lesion location might impact on their executive deficits. These deficits were also measured with the BADS subtests as well as with seven standard executive tests previously reported as indicative for anterior damage (Stuss & Alexander, 2000; Stuss & Levine, 2002; Alvarez & Emory, 2006). An additional goal of the present study was to investigate which BADS executive subtests show more impairment in patients with anterior lesions in comparison to patients with posterior lesions and find the most sensitive and specific BADS variables for the detection of anterior pathology.

Methods

Participants
Fifty two patients participated in this study. Forty one of these were in treatment at the ‘Anagennisi’ Rehabilitation Center in Nea Redestos, Thessaloniki, Greece. The other 11 were recruited from the neurosurgery department of the Saint Lukas Clinic in Panorama, Thessaloniki, Greece.

Inclusion Criteria
With regard to our first purpose, all patients included in this study had documented brain injury with lesions localized in anterior or posterior brain regions, verified on CT and/or MRI-scans. Thirty patients had anterior (frontal/frontotemporal or anterior subcortical) lesions (AL group), whereas 22 patients had focal posterior (parietal/occipital) lesions (PL group). More specifically, of the 30 patients with lesions to anterior cerebral areas, 13 had sustained a traumatic brain injury with predominantly prefrontal damage (6 mainly left hemispheric, 7 predominantly right hemispheric), 8 patients had a stroke in frontal or frontotemporal brain regions, including 5 patients
with a subcortical stroke in the basal ganglia (3 patients had an haemorrhagic stroke in the left hemisphere, 2 a right-sided haemorrhagic stroke, and 3 patients a right-sided ischemic stroke). We included patients with anterior basal-ganglia lesions because of the connections between the basal ganglia and the frontal cortex and their relation with executive dysfunction (e.g. Godefroy, 2003; Heyder et al., 2004). The AL group also included 9 patients who had undergone anterior (frontal-fronto-temporal) lobectomies as part of tumour surgery (3 left hemispheric and 6 right hemispheric).

Of the 22 patients with posterior lesions, four patients had focal parietal or occipital damage, or combined parietal-occipital damage in these posterior brain regions due to a traumatic brain injury (1 in the left hemisphere, 3 in the right hemisphere), 10 patients had sustained a stroke confined to parietal and parietal-occipital brain areas (1 with an ischemic stroke in the left hemisphere, 2 with a right-sided haemorrhagic stroke and 7 with a right-sided ischemic stroke) and 8 patients had undergone posterior lobectomies as part of tumour surgery (5 left hemispheric, 3 right hemispheric).

All patients were at least 6 months post-onset when assessment took place (time since injury ranged from 6 to 46 months, M = 11.5 months, SD = 8.508). Traumatically injured patients and patients with a haemorrhagic stroke had experienced a loss of consciousness following brain damage and the duration of coma ranged from 7 to 24 days (coma duration, M = 15.83, SD = 4.99). The duration of post-traumatic amnesia (PTA) in TBI patients ranged from 14 to 67 days (PTA duration, M = 32.88, SD = 18.38). All patients (TBI, stroke, tumour) participating in this study were inpatients with severe motor and sensory impairments at the time of onset (TBI, stroke) or after surgery (tumours). These sensorimotor deficits required clinical physiotherapy for at least three months. Additional medical information was available for 11 stroke patients: 8 with posterior lesions had a history of uncontrolled hypertension and 3 (1 AL and 2 PL) had a history of atrial fibrillation. Among the post-surgery tumour patients, 9 (4 AL and 5 with PL) had a history of persistent epilepsy, whereas 8 (5 AL and 3 PL) had suffered a sudden seizure with loss of consciousness prior to surgery.

Patients with progressive neurological disease, severe behavioural disorders, severe verbal, sexual or aggressive disinhibition, severe loss of initiative (aboulia), lack of awareness of deficit (anosognosia), severe aphasia, severe hemi-inattention, previous psychiatric disorders and substance abuse, were excluded from the study. The exclusion of patients with severe behavioural problems was mostly related to their difficulties in cooperating with the examiner, the lack of involvement in the assessment process and the inability to complete the tasks used in the present study. None of our patients had visual-field defects that interfered with the administration of the tests as verified in their medical records.
A control group of 29 healthy adults was recruited via the patients’ relatives and the researcher’s environment. None of the healthy controls had a history of neurologic or psychiatric disease (self-report). The female/male ratio for the patients groups was 28/22, whereas it was 18/11 for the controls.

Mean Scores and SDs, as well as statistical tests for demographic data and IQ are presented in Table 1. No significant group differences were found among the three participant groups with respect to age (ranging from 18-61 years), educational level (ranging from 9-17 years), handedness as assessed with the Annett Hand Preference Questionnaire (Annett and Kilshaw, 1983) or general intellectual ability based on the participants’ performance on Raven’s Standard Progressive Matrices.

All brain-injured patients selected for this study were also signalled by their therapists (mostly physiotherapists and speech-therapists) for having executive difficulties in their everyday activities and during therapeutic sessions. Subsequently, the same therapists were asked to observe these problems, using a Greek translation of Spikman’s Checklist of Executive Disorders (Spikman, 2002). This checklist consists of 2 parts, a cognitive part and a section with social and awareness questions. Nine “cognitive” items ask about difficulties in daily life with working memory (in particular mental manipulation of information), attention (like distractibility and divided attention), planning and execution, decision making and reasoning, abstraction, problem-solving, flexibility, initiative and insight. Three items assess the presence of social problems like interpersonal difficulties, problems at work, and troubles with social contacts and leisure. Two separate questions evaluate the awareness of executive problems of patient and of proxies. Every item can be

### Table 1

Mean scores (+SDs), demographic data and estimated IQ for AL patients, PL patients and HCs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Anterior M (SD) (n = 30)</th>
<th>Posterior M (SD) (n = 22)</th>
<th>Healthy M (SD) (n = 29)</th>
<th>df</th>
<th>F and p (1-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41.47 (15.40)</td>
<td>48 (10.73)</td>
<td>41.72 (13.02)</td>
<td>(2, 80)</td>
<td>F = 1.828, p = .167</td>
</tr>
<tr>
<td>Education</td>
<td>12.97 (2.07)</td>
<td>12.5 (2.11)</td>
<td>13.10 (2.22)</td>
<td>(2, 80)</td>
<td>F = .52, p = .591</td>
</tr>
<tr>
<td>PM (IQ)</td>
<td>103.53 (6.458)</td>
<td>105.86 (5.222)</td>
<td>106.62 (6.652)</td>
<td>(2, 80)</td>
<td>F = 1.951, p = .149</td>
</tr>
</tbody>
</table>

AL: patients with anterior lesions; PL: patients with posterior lesions; HCs: healthy controls; PM: Raven’s Progressive Matrices estimated IQ scores.
answered with yes (problem present) or no. The therapists were familiar with the patients, having worked with them for several months. The procedure was blind, as therapists did not have any information about lesion location.

Materials:
Standard Executive measures
All participants also underwent an extensive neuropsychological assessment of executive functions. For this purpose, seven executive measures derived from the standard version of the WCST (Heaton, 1981), a Greek version of the Stroop Word Colour Test (Zalonis et al., 2009), a Greek version of the Verbal Fluency Test (Kosmidis et al., 2004), a Greek version of the Trail Making Test (Zalonis et al., 2008) and the Digit Span Backward subtest from the Wechsler Adult Intelligence Scale-III (WAIS-III, Wechsler, 1997) were administered. These standard executive tests were chosen because they are widely used as measures of executive functioning and they were found to be sensitive indicators of anterior brain damage (Eslinger & Grattan, 1993; Stuss et al., 1998; Troyer et al., 1998; Barcelo et al., 2000; 2001; Barcelo & Knight, 2002; Stuss et al., 2000; Stuss & Alexander, 2000; Miller & Cohen, 2001; Stuss et al., 2001; Greve et al., 2002; Stuss and Levine, 2002; Bennett et al., 2005; Alvarez & Emory, 2006). The seven standard executive tests included in the present study yielded the following variables: 1) WCST number of correct categories – WCSTCat, 2) number of WCST perseveration errors – WCSTPersev., 3) WCST ratio of perseveration errors compared to the total trials completed – WCSTPersev/tot, 4) Stroop Word Colour Interference condition – StroopInterf., 5) ratio of Phonemic Fluency Score (total number of correct words generated) compared to Semantic Fluency Score – VFP/S, 6) Trail Making Test ratio of time to complete part B compared to the time to complete part A (TMT B/A) and 7) Digit Span Backward (DigitB).

Memory and language tests
In order to verify that the patients’ complaints and performances on executive tests were mainly affected by executive disabilities rather than other consequences of brain damage (like memory or comprehension problems) a set of memory and language tests was also administered. These control measures included the Digits Forward (DigitF) subtest from the Wechsler Adult Intelligence Scale-III (WAIS-III, Wechsler, 1997a), the Rey Auditory Verbal Learning Test (RAVLT, Messinis et al., 2007, variables: first trial (RAVLT1), total list learning trials 1-5 (RAVLT1-5), short-delayed recall (RAVLTSR), long – delayed recall (RAVLTDLDR) and Recognition trial (RAVLTRrecog), the Rey-Osterrieth Complex Figure Test (ROCFT, Osterrieth, 1944, variables: immediate recall (ROCFTImR), delayed recall (ROCFTD) and recognition (ROCFTRecog), the Vocabulary subtest of the WAIS-III (Wechsler, 1997a) and the Boston Naming Test – Short Form (BNT) (Tsapkini & Emmanuel, 2007).
BADS Executive battery
All participants completed the BADS, with task instructions and materials translated into Greek for research purposes. The following scores were recorded: 1) the Rule Shifting Test Raw Score – BADSRULE, 2) the BADS Action Program Test Raw Score – BADSACTION, 3) the BADS Key Search Test Raw Score - BADSKEY, 4) the BADS Time Judgment Raw Score - BADSTJ, 5) the BADS Zoo Map Test Condition 1 Raw Score - BADSZoo1, 6) the BADS Zoo Map Test Condition 2 Raw Score – BADSZoo2, 7) the total Zoo Raw Score – BADSZoo, and 8) the BADS Modified Six Elements Test Raw Score – BADSMSET. Planning and total time of the BADS Zoo conditions were additional executive measures used to deepen the analysis of the BADSZoo variable.

Both standard and ecologically valid executive variables derived from the BADS were chosen to represent various aspects of executive functions, such as planning and organizing, problem solving, cognitive flexibility, set shifting, updating/working memory abilities, self-monitoring and control of action, reasoning, inhibition, initiation and sequencing.

Procedure
All the patients underwent three or more testing sessions. The total time to complete all the tests took approximately four to five hours. All the tests were also administered to the healthy controls in two testing sessions, each lasting approximately 1½ hour. The order of administration of the tests was fixed (first the standard executive, memory and language tests and later the BADS executive subtests).

Statistical Analyses
Prior to analysis, the distribution of the scores was examined using Shapiro-Wilk’s normality tests. Executive, memory and language variables found to be non-normally distributed were thereupon transformed and tested again for normality. Negatively skewed variables were transformed using square transformation ($x^2$), whereas for positively skewed the square root transformation was used (Carter, 1997). The normalised transformed variables ($t^*$) were analysed using parametric statistical tests (one-way ANOVA), whereas the scores that remained non-normally distributed were analysed with non-parametric tests (Kruskal-Wallis tests). Mann-Whitney U-tests were used for post-hoc multiple comparisons among the three participant groups (anteriorly lesioned patients, posteriorly lesioned patients and healthy controls). All the executive variables were found to be non-normally distributed and stayed so after transformation because of violation of the homogeneity of variances comparisons. Effect sizes were computed for parametric comparisons using $\eta^2_p$. Effect sizes for non – parametric post-hoc comparisons were also computed using an approximate value of $r$. This $r$ value was calculated by dividing the value of $z$ in the Mann – Whitney test by the square root of $N$ (Field, 2005). The effect sizes were
reported according to Cohen’s (1988) criteria (.1 = small effect, .3 = medium effect, .5 = large effect).

Another goal of the present study was to investigate which set of BADS executive variables are the best predictors of executive dysfunction related to anterior brain damage in order to develop a more accurate executive battery for patients with executive deficits related to anterior lesions, such as TBI patients. Therefore, firstly we conducted Kruskal-Wallis tests and then post-hoc Mann-Whitney U multiple comparisons to explore the differences between the three groups (anteriorly lesioned patients, posteriorly lesioned patients and healthy controls) in both standard and BADS variables. Post-hoc power analyses of all the statistically significant Mann–Whitney (two-tailed) pair-wise comparisons between the two patient groups (and between the healthy controls and each of the patient groups) were also computed using the Observed power (1-β) of the SPSS General Linear Model. We also investigated which BADS variables were most effective in predicting group membership (anterior or posterior pathology). To this aim, the BADS measures found to be sensitive and specific to anterior lesion were entered in a stepwise logistical regression analysis using a Forward: LR approach.

Results

Table 2 presents the mean scores (and SDs) and the results of the statistical analyses for the memory and language variables. No significant group differences were found between the three participant groups on these variables (p > .05). Parametric Dunnett t-tests (two-sided) multiple comparisons only showed significant group differences between patients with anterior lesions and healthy controls on the total list learning variable RAVLT1-5 (mean difference = 4.90, p = .010, η² = .54). Nonparametric Mann-Whitney multiple comparisons only revealed significant group differences between the AL group and healthy controls on the short-delayed recall trial (RAVLTSDR) (z = -2.564, p = .010, r = .30) and the long-delayed recall trial (RAVLTLDLR) (z = -2.773, p = .006, r = .31) of the RAVLT as well as on the recognition trial of the ROCFT (ROCFTRecog) (z = -2.497, p = .013, r = .27), with the AL group presenting worse performances. Impaired learning and short-term recall (with interference) of the AL group can be attributed to deficits in working memory and retrieval processes, as well as to a failure in interference control, both closely related to anterior executive dysfunction (Stuss & Levine, 2002). Poor long-term recall of the same patient group could be explained by the limited amount of information previously maintained in short-term storage. Statistical analyses of the therapists’ Checklist ratings, using independent sample t-tests, showed that the therapists rating patients with anterior lesions reported significantly more daily dysexecutive symptoms (M =
Table 2 Mean scores (+SDs) and results of parametric and non-parametric comparisons among the three participant groups for memory and language variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Anterior (n = 30)</th>
<th>Posterior (n = 22)</th>
<th>Healthy (n = 29)</th>
<th>df</th>
<th>F and p (1-tailed)</th>
<th>Post-hoc comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>tVocabulary</td>
<td>44.76 (6.96)</td>
<td>47.86 (7.005)</td>
<td>48.72 (8.11)</td>
<td>(2,80)</td>
<td>F = 2.552</td>
<td>1*, 2, 3</td>
</tr>
<tr>
<td>BNT</td>
<td>12.8 (1.06)</td>
<td>13.36 (1.13)</td>
<td>13 (1.16)</td>
<td>(2,80)</td>
<td>χ² = 3.410</td>
<td>1*, 2, 3</td>
</tr>
<tr>
<td>DigitF</td>
<td>9.8 (1.42)</td>
<td>10.31 (1.42)</td>
<td>10.24 (1.47)</td>
<td>(2,80)</td>
<td>χ² = 2.791</td>
<td></td>
</tr>
<tr>
<td>RAVLT1</td>
<td>7.2 (0.84)</td>
<td>7.72 (1.54)</td>
<td>7.79 (1.87)</td>
<td>(2,80)</td>
<td>χ² = 3.206</td>
<td></td>
</tr>
<tr>
<td>RAVLT1-5</td>
<td>51.13 (5.74)</td>
<td>55.00 (6.05)</td>
<td>56.03 (7.57)</td>
<td>(2,80)</td>
<td>F = 4.541</td>
<td>1*, 2, 3</td>
</tr>
<tr>
<td>RAVLTSDR</td>
<td>11.33 (1.86)</td>
<td>12.40 (1.50)</td>
<td>12.48 (1.76)</td>
<td>(2,80)</td>
<td>χ² = 7.971</td>
<td>1*, 2, 3</td>
</tr>
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<td>RAVLTLDR</td>
<td>10.76 (1.69)</td>
<td>11.95 (1.73)</td>
<td>12.06 (1.7)</td>
<td>(2,80)</td>
<td>χ² = 8.661</td>
<td>1*, 2, 3</td>
</tr>
<tr>
<td>RAVLTRec.</td>
<td>12.5 (1.54)</td>
<td>13.09 (1.26)</td>
<td>13.44 (1.21)</td>
<td>(2,80)</td>
<td>χ² = 5.89</td>
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<tr>
<td>ROCFTImR</td>
<td>19.83 (3.96)</td>
<td>21.36 (4.08)</td>
<td>22.45 (3.99)</td>
<td>(2,80)</td>
<td>F = 3.165</td>
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<tr>
<td>ROCFTDR</td>
<td>18.36 (4.01)</td>
<td>19.77 (4.16)</td>
<td>20.93 (3.55)</td>
<td>(2,80)</td>
<td>F = 3.141</td>
<td></td>
</tr>
<tr>
<td>ROCFTRec.</td>
<td>9.8 (1.39)</td>
<td>10.68 (1.42)</td>
<td>10.72 (1.19)</td>
<td>(2,80)</td>
<td>χ² = 7.451</td>
<td>1*, 2, 3</td>
</tr>
</tbody>
</table>

Anterior: patients with anterior lesions, Posterior: posteriorly lesioned patients, t = transformed, BNT: Boston Naming Test-Short Version in Greek (Tsapkini and Emmanouel, 2007), DF: Digits Forward, WAIS-III, RAVLT1: the first trial of a Greek Version of the Rey Auditory Verbal Learning Test (Messinis et al., 2007), RAVLT 1-5: the total list learning trials 1-5 of the RAVLT, RAVLTSDR: the short-delayed recall of the RAVLT, RAVLTLDR: the long–delayed recall trial of the RAVLT, RVLTRecog: recognition trial of the RAVLT, ROCFTImR: immediate recall trial of the Rey Osterrieth Complex Figure Test-ROCFT, ROCFTDR: the delayed-recall trial of the ROCFT, ROCFTRecog: the recognition trial of the ROCFT.

* Significant difference (Bonferroni adjustment α = .017).
1 HCs > AL patients
2 HCs > PL patients
3 AL patients < PL patients
5.43, SD = 1.47) than the therapists of the posteriorly - damaged patients (M = 3.27, 1.12). This was the case with regard to the cognitive aspects [t (50) = 5.746, p = .000] as well as to the social and emotional executive aspects of the Checklist [AL group: M = 1.97, SD = 1.18, PL group: M = .56, SD = .58, t (50) = 5.825, p = .000].

Table 3 shows the Kruskal – Wallis results of the standard executive variables among the three participant groups. The results indicate significant group differences in all the standard executive variables among the three groups (all p = .000). Post-hoc multiple comparisons using Mann-Whitney U tests (two-tailed), were conducted for pair-wise comparisons between the three participant groups. The results of these comparisons are also presented in Table 3. Bonferroni corrections (a= .05/3 = .017) were used for the control of Type 1 error across tests. Effect sizes were calculated to express the standardized magnitude of the difference between the group means, along with the power value for all the statistically significant differences between groups. Post-hoc analysis revealed that healthy controls (HCs) performed better than AL patients on all the standard executive variables (all z > -3.523, all p = .000, r = .52 - .712, power = .981 – 1.00). HCs were also better than the posteriorly lesioned patients on almost every standard executive variable (all z > -2.435, all p < .015, r= .14 - .43, power = .474 - .992) except for the TMTB/A ratio (z = -1.284, p = .199) and the Digit Span Backward (z = .638, p = .523). Finally, significant group differences between the two patient groups, with significantly worse performances for the AL group, were found in almost all the standard executive variables (all z > -3.149, all p < .002, r= .25 - .46, power = .815 - .998) apart from the StroopInterf (z = -2.173, p = .036) and the VFP/S ratio. These results are in agreement with the therapists’ observations, showing that patients with posterior lesions also show executive problems, albeit to a significantly lesser degree than patients with anterior lesions.

Additional analyses of simple speed tests such as the Trail Making Test A (TMTA) and the Stroop Color Condition did not yield significant differences between the two patient groups: in the TMT A (AL group: M = 74,27, SD = 27; PL group: M = 81.59, SD = 42.87) (z = – .787, p = .431, r = .109) or in the Stroop Color Condition (AL group: M = 59.67, SD = 12.88; PL group: M = 66.32, SD = 10.92) (z = – 1.808, p = .071, r = .25). These results indicate that the anterior group faces more specific difficulties in executive functioning than general cognitive dysfunction.

Finally, the results of the BADS executive variables for the three participant groups are presented in table 4. Significant group effects were found on all the executive subtests of the BADS (all ps < .005). Further multiple post-hoc comparisons between two groups using 2-tailed Mann-Whitney U tests were performed with Bonferroni correction (α= .017) for the control of Type 1 errors across tests. Effect sizes were computed that express the standardized magnitude of the difference between the group means (r). Here also, power values of all the significant differences were calculated .The results revealed that the HCs performed significantly better than the
AL group on all the variables of the BADS, (all zs > -3.137, all ps < .002, r= .34 - .69, power = .917 - .100), and significantly better than the PL group on the BADSRULE, the BADSACTION, the BADSKEY, the BADSZoo1 and the BADSZoo (all zs > -2.539, all ps < .011, r= .28 - .39, power = .718 - .996). Additionally, Mann-Whitney post-hoc analyses revealed that the AL group performed significantly worse than the PL group on every BADS variable [all zs > -2.431, all ps < .015, r= .30 - .49, power = .545 - 1.00], except for the BADSTJ (z = -1.639, p= .101) and the BADSZoo1 (z = -1.854, p = .064) [the same absence of significant differences was found between the two patient groups for the BADSZoo1 planning time variable (z = -.435, p = .663)]. With regard to the sensitivity and specificity issue, no significant differences were found

<table>
<thead>
<tr>
<th>Test comparisons</th>
<th>Anterior M (SD) (n = 30)</th>
<th>Posterior M (SD) (n = 22)</th>
<th>Healthy M (SD) (n = 29)</th>
<th>χ² and p (1-tailed)</th>
<th>Post-hoc comparisons 1 2 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>DigitB</td>
<td>6.63 (1.24)</td>
<td>7.95 (1.67)</td>
<td>8.2 (1.67)</td>
<td>χ² = 14.823</td>
<td>1*, 2, 3*</td>
</tr>
<tr>
<td>TMTB/A</td>
<td>3.11 (1.24)</td>
<td>2.25 (0.71)</td>
<td>1.92 (0.54)</td>
<td>χ² = 23.568</td>
<td>1*, 2, 3*</td>
</tr>
<tr>
<td>StroopInterf.</td>
<td>-6.68 (6.83)</td>
<td>-2.1 (4.13)</td>
<td>3 (2.65)</td>
<td>χ² = 30.067</td>
<td>1*, 2*, 3</td>
</tr>
<tr>
<td>WCSTCat.</td>
<td>2.56 (1.67)</td>
<td>4.81 (4.13)</td>
<td>5.96 (2.65)</td>
<td>χ² = 48.181</td>
<td>1*, 2*, 3*</td>
</tr>
<tr>
<td>WCSTPersev.</td>
<td>0.67 (25.00)</td>
<td>32.68 (24.95)</td>
<td>13.41 (9.77)</td>
<td>χ² = 44.381</td>
<td>1*, 2*, 3*</td>
</tr>
<tr>
<td>WCSTPersev/ tot.</td>
<td>0.63 (0.22)</td>
<td>0.38 (0.26)</td>
<td>0.24 (0.25)</td>
<td>χ² = 27.781</td>
<td>1*, 2*, 3*</td>
</tr>
<tr>
<td>VFP/S</td>
<td>0.53 (0.13)</td>
<td>0.54 (0.14)</td>
<td>0.68 (0.08)</td>
<td>χ² = 3.170</td>
<td>1*, 2*, 3</td>
</tr>
</tbody>
</table>

* Significant difference (Bonferroni adjustment α = .017).
1 HCs > AL patients
2 HCs > PL patients
3 AL patients < PL patients
between the PL group and the healthy control group on the BADSMSET \((z = -2.312, \ p = .021)\) and the BADSZoo2 \((\text{all } z < -1.367, \ p = .172)\).

In summary, the multiple comparisons showed significantly better performances of the healthy control group in comparison to patients with anterior lesions as well as in comparison to the PL group on the BADSZoo1, whereas no significant group differences were found between the two patient groups on this executive variable.

In addition, our results revealed significantly better performances of the HCs in comparison to the AL group as well as in comparison to the PL group on the BADSRULE, the BADSACTION, the BADSKey and the BADSZoo. Significant

Table 4  Mean raw Scores \((\pm \text{SDs})\), and results of non-parametric comparisons between the HCs and the AL patients, between the HCs and the PL patients and between the two patient groups for the BADS executive variables.

<table>
<thead>
<tr>
<th>Test</th>
<th>Anterior M (SD) ((n = 30))</th>
<th>Posterior M (SD) ((n = 22))</th>
<th>Healthy M (SD) ((n = 29))</th>
<th>df</th>
<th>(\chi^2) and (p)</th>
<th>Post-hoc Comparisons:</th>
</tr>
</thead>
<tbody>
<tr>
<td>BADSRULE</td>
<td>4.00 (3.08)</td>
<td>1.40 (1.76)</td>
<td>0.10 (0.40)</td>
<td>2</td>
<td>(\chi^2 = 40.69)</td>
<td>1*, 2*, 3*</td>
</tr>
<tr>
<td>BADSACTION</td>
<td>3.2 (0.96)</td>
<td>4.18 (0.79)</td>
<td>4.68 (0.47)</td>
<td>2</td>
<td>(\chi^2 = 34.34)</td>
<td>1*, 2*, 3*</td>
</tr>
<tr>
<td>BADSKey</td>
<td>8.8 (2.61)</td>
<td>11.09 (3.44)</td>
<td>14.17 (1.3)</td>
<td>2</td>
<td>(\chi^2 = 38.61)</td>
<td>1*, 2*, 3*</td>
</tr>
<tr>
<td>BADSTJ</td>
<td>3.4 (0.72)</td>
<td>3.72 (0.45)</td>
<td>3.89 (0.3)</td>
<td>2</td>
<td>(\chi^2 = 10.43)</td>
<td>1*, 2, 3</td>
</tr>
<tr>
<td>BADSZoo1</td>
<td>3.76 (2.01)</td>
<td>5.090 (2.505)</td>
<td>7.41 (0.82)</td>
<td>2</td>
<td>(\chi^2 = 35.93)</td>
<td>1*, 2*, 3</td>
</tr>
<tr>
<td>BADSZoo2</td>
<td>6.7 (1.6)</td>
<td>7.63 (1.13)</td>
<td>7.96 (0.18)</td>
<td>2</td>
<td>(\chi^2 = 25.87)</td>
<td>1*, 2, 3*</td>
</tr>
<tr>
<td>BADS Zoo</td>
<td>10.46 (3.15)</td>
<td>12.77 (3.08)</td>
<td>15.37 (0.90)</td>
<td>2</td>
<td>(\chi^2 = 39.151)</td>
<td>1*, 2*, 3*</td>
</tr>
<tr>
<td>BADSMSET</td>
<td>4 (0.98)</td>
<td>5.40 (0.85)</td>
<td>5.86 (0.85)</td>
<td>2</td>
<td>(\chi^2 = 45.623)</td>
<td>1*, 2, 3*</td>
</tr>
</tbody>
</table>

* Significant difference \((\text{Bonferroni adjustment } \alpha = .017)\). 1 HCs > AL patients; 2 HCs > PL patients; 3 AL patients < PL patients
differences were found between the two patient groups on the same executive variables as well, with the posteriorly-lesioned patients exhibiting better performances.

Finally, the AL group performed worse than both the PL group and the healthy controls on the BADSZoo2 and the BADSMSET, whereas no significant group differences were found between the PL group and the HCs on the same variables. Further analyses of the BADSZoo2 revealed that the AL group was significantly slower in the planning time variable of this condition than the two other participant groups [AL group < PL group: \( z = -2.462, p = .014 \), AL group < HCs group: \( z = -3.911, p < .0005 \)]. No significant differences were found between the PL patients and the healthy controls on the same variable (HCs group = PL group: \( z = 2.170, p = .030 \)).

A stepwise logistic regression analysis (forward: LR method) was conducted in order to find the best predictors of group membership (AL or PL) among the BADS variables previously found to be sensitive and specific to anterior pathology.

The model contained 6 independent BADS executive variables the BADSRULE, the BADSACTION, the BADSKEY, the BADSZoo, the BADSZoo2 and the BADSMSET as potential predictors of group membership. The results of the logistic regression analysis are presented in table 5.

The regression model was significant on step 1 \( \chi^2 (1, N = 52) = 23.064, p = .000 \), with only the BADSMSET variable having a significant impact on the dependent variable “lesion location”. The probability of the Wald statistic for the BADSMSET independent variable was significant \( \chi^2 (1, N = 52) = 13.968, p = .000 \)

### Table 5

<table>
<thead>
<tr>
<th>Step 1 Variables in the Equation</th>
<th>( \beta )</th>
<th>S.E</th>
<th>Wald</th>
<th>( p )</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>BADSMSET</td>
<td>1.576</td>
<td>.422</td>
<td>13.968</td>
<td>.000*</td>
<td>4.834</td>
</tr>
<tr>
<td>Constant</td>
<td>-7.810</td>
<td>2.086</td>
<td>14.023</td>
<td>.000</td>
<td>.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 1 Variables not in the Equation</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>BADSRULE</td>
<td>.242</td>
</tr>
<tr>
<td>BADSACTION</td>
<td>.136</td>
</tr>
<tr>
<td>BADSKEY</td>
<td>.725</td>
</tr>
<tr>
<td>BADSZoo2</td>
<td>.823</td>
</tr>
<tr>
<td>BADSZoo</td>
<td>.390</td>
</tr>
</tbody>
</table>

* statistical significant
and BADSMSET discriminated anteriorly and posteriorly lesioned patients with an accuracy of 78.8%. These results are in agreement with our previous multiple Mann-Whitney comparisons, indicating that poor performance on the BADSMSET is specifically associated with the presence of anterior brain damage. Multicollinearity of the independent variables was not further investigated, as the logistic regression analysis included the BADSMSET as the only variable in the equation.

**Discussion**

In the present study we examined the validity of the BADS executive subtests in relation to anterior executive dysfunction. After finding the most sensitive and specific BADS executive test variables, we also investigated which of these variables could accurately predict anterior brain pathology. Prior to this, as part of the recruitment procedure, we verified that all the patients participating in our study had dysexecutive problems. Therefore, the patients were observed and rated with Spikman’s Executive Checklist and tested with several neuropsychological tests. Analysis of the therapists’ ratings revealed that Spikman’s Executive Checklist identifies more dysexecutive problems in patients with anterior lesions than in posteriorly injured patients. This indicates that a basic checklist can be quite accurate in assessing the role of anterior brain regions in executive functioning. Unquestionably, further research is needed in order to investigate this discriminatory function of behavioral rating scales of executive functioning.

A set of memory and language tests were also administered as control measures in order to ascertain that patients’ performance on executive tests is mainly affected by executive impairments rather than other impact of brain injury. Non – significant differences found between AL and PL groups in the majority of the memory and language variables. The use of seven standard executive variables sensitive to AL confirmed the results of previous studies with regard to the primary effect of anterior pathology on executive test performance. Specifically, our results show that all standard executive tests are sensitive to anterior brain lesions except for the StroopInterf condition and the VFPhonemic/Semantic ratio, whereas TMT B/A ratio and DigitBack are more specific in identifying patients with anterior lesions. Our analyses also revealed that significant differences between the two patient groups in almost all the executive variables had sufficient power. Additional analyses of simple speed tests such as the Trail Making Test A (TMTA) and the Stroop Colour Condition revealed non-significant differences between the two patient groups. These findings along with the non – significant results between AL and PL groups the two patient groups in almost all memory and language variables show that the significantly poorer performances of the anterior group compared to those of the posterior one on
almost all the executive measures reflect more specific difficulties in executive functions rather than a more general/severe cognitive dysfunction.

Therefore, with respect to our first goal, the results show significant group differences in performance between patients and healthy controls on almost every BADS executive variable, confirming the results of previous studies suggesting that the BADS is a useful tool to detect brain damage. Significant group differences were also found between healthy controls and patients with anterior lesions, as well as between healthy controls and posteriorly lesioned patients on the BADSZoo1 (total raw score), whereas the two patient groups did not differ on this variable. This finding suggests that the BADSZoo1 identifies people experiencing executive problems after brain damage, but cannot adequately discriminate patients with anterior from those with posterior lesions. Therefore, poor performance on this BADS variable only indicates the presence of brain pathology but does not specifically indicate the location of brain injury.

A possible explanation for this result is that the BADSZoo1 requires flawless visuospatial abilities and complex visual scanning skills that rely on intact posterior brain regions. Therefore, patients with anterior lesions may exhibit impaired performance on this task due to executive planning difficulties, whereas posteriorly-injured patients might perform inadequately due to content-specific visuospatial impairments or slowness in visual scanning. The present results are in agreement with previous lesion and neuroimaging studies indicating recruitment of posterior regions involved in basic linguistic or perceptual operations of standard executive tasks. (Stuss & Levine, 2002). Thus, our findings suggest that performance on the BADSZoo1 may be affected by the more “content-specific” aspects of executive tasks. In other words, participants may show impairments in task-specific processes, rather than deficits in anterior executive dysfunctioning (Stuss & Levine, 2002; Alvarez & Emory, 2006; Packwood et al., 2011).

Our results also show that the BADSRULE, the BADSACTION, the BADSKEY and the BADSZoo (total raw scores for each variable) are sensitive to anterior pathology since they adequately discriminate anteriorly from posteriorly damaged patients. However, these variables also discriminate healthy controls from patients with posterior lesions. This suggests that these four BADS variables are sensitive but not specific for anterior brain damage. Poor performance on these variables is associated with brain pathology and is more prominent following anterior brain pathology, which is in line with decreasing executive abilities in daily functioning (as measured using the clinicians' ratings in Spikman’s Checklist). Our results substantiate the findings of previous lesion and neuroimaging studies that executive tests are multifactorial and engagement in these tests cannot be solely attributed to anterior damage (Duncan et al., 1995; 1997; Baddeley, 1996; Burgess et al., 1998; Stuss & Alexander, 2000; Stuss & Levine, 2002; Bennett et al., 2005; Alvarez & Emory, 2006; Collette et al., 2006).
More importantly, the present results revealed that patients with anterior lesions performed significantly worse than both the posteriorly lesioned group and healthy controls on the Zoo2 and the MSET from the BADS. No significant group differences for the same variables were found between healthy controls and the posteriorly damaged group. This suggests that the BADSZoo2 and the BADSMSET are two ecologically valid executive variables that seem to be more accurate and specific indicators of anterior damage, when compared with all the other BADS variables investigated in this study.

Particularly, with respect to the somewhat surprising finding of the BADSZoo2 as a better indicator of anterior damage than the BADSZoo1, this could be interpreted as an interference effect from Condition 1 on Condition 2 of the BADSZoo. Before formulating a route in Condition 1, the participants look at the Zoo Map for the first time, and have to visually scan the places to be visited. This visual scanning is served by posterior regions in the brain. Therefore, slowness in visual scanning may explain the poor performance of the posteriorly lesioned patients in Zoo map Condition 1. Then, the participant has to formulate a plan and follow the route by drawing a continuous line without breaking test rules. In this stage, the task demands more executive control, which is related to anterior brain areas. Patients with anterior lesions were observed to lose more points as they were often imposed penalties for rule breaking. Previous lesion studies confirm the presence of rule breaking behaviour and inhibition problems after anterior damage (Burgess et al., 1998). Thus, the poor performance of both posteriorly and anteriorly injured patients on Condition 1 may be attributed to different cognitive deficits (i.e. visual scanning and/or rule breaking). The same Zoo Map is shown again in Condition 2, which reduces visual scanning requirements. In this condition participants are already familiar with the map and this may contribute to a swifter visual processing by patients with posterior lesions. Even though Condition 2 has lower executive demands, patients with anterior injury still made many rule breaking errors (as in Condition 1) and our results show that they also needed more planning time than posteriorly damaged patients.

More importantly, a regression analysis on sensitive and specific BADS subtests revealed that only the BADSMSET was a significant predictor of anterior pathology. BADSMSET was a better predictor than the BADSZoo2 and it could correctly discriminate posteriorly from anteriorly injured patients in 78.8 % of the cases. This result supports the findings of a factor analytical study conducted by Burgess et al. (1998), in which the Six Element Test was found to be strongly related to intentionality and inhibition, two primary executive processes specifically associated with “pure” frontal lobe executive dysfunction (Andres, 2003).

In conclusion, our findings provide new information for clinicians and researchers about the relation between ecologically valid executive measures and brain dysfunction. In detail, the ecological BADSMSET subtest could be used as a
screening tool in its own right (with some confidence respectively to neuroimaging) for the differential diagnosis of anterior pathology. Additionally, the BADSMSET can provide useful information with respect to the qualitative indices of the specific executive dysfunction related to anterior damage, e.g. intentionality and inhibition. This additional information cannot be adequately provided from neuroimaging data. Moreover, this BADS subtest is of special clinical importance as it indicates that the executive processes that it measures (intentionality and inhibition) are more severely impaired in patients with anterior lesions. Deficits measured by other BADS subtests might partially overlap in patients with anterior and more posterior lesions. For clinicians this means that intentionality and inhibition are more severely disturbed in patients with anterior lesions and that they will have to design their individualized rehabilitation programs accordingly. Programs that also include behavioural interventions seem more appropriate for these impairments than purely cognitive treatments (Burgess et al., 1998; 2006).

Finally, from a more practical perspective, the BADSMSET (and the BADSZoo2) seem to be appropriate for a more accurate and less-time demanding (and thus more cost-effective) neuropsychological assessment of executive dysfunction in patients with mainly anterior damage, such as patients with traumatic brain injury. Reduction of the number of to-be-administered tests is also preferable because the likelihood of false-positive results increases when the number of administered tests grows (Burgess, 2003; Boelen et al., 2009).
References


Tsapkini, K., Emmanouel, A., Passalidou C., and Nasiopoulou, G. Boston Diagnostic Aphasia Examination—Short Form: Greek normative data. 9th European Conference on Psychological Assessment and 2nd International Conference of the Psychological Society of Northern Greece; 3-6 May 2007; Thessaloniki, Greece.


3

Validity of the Dysexecutive Questionnaire (DEX).
Ratings by brain-injured patients and their therapists

Published as:
Abstract

Objective: We investigated the validity of the DEX-Questionnaire (both completed by patients, DEX-Self, and by therapists, DEX-TH), included in the Behavioural Assessment of the Dysexecutive Syndrome (BADS), at identifying differences in the severity of dysexecutive symptoms according to lesion location. We also examined the strength of associations of the DEX-Self and the DEX-TH reports with the subtests of the BADS as well as two other real-life executive tasks, the Everyday Description Task and the Twenty Question Test.

Method: We compared 30 patients with anterior lesions (AL) to 22 patients with posterior lesions (PL). Twenty-nine healthy participants and their relatives were included as controls.

Results: Significant group differences were found only on the DEX-TH, but not on the DEX-Self, indicating poor insight in patients with AL. The DEX-TH were revealed accurate in detecting more severe dysexecutive symptoms in the AL group. Furthermore, only the DEX-TH reportings were significantly correlated with the above executive tests. Multiple regression analysis showed that the Modified Six Elements Test, a subtest of the BADS, predicted DEX-TH as accurately as the total BADS.

Conclusion: The DEX-TH reportings and the MSET can provide valuable information about the severity of daily executive dysfunctioning with implications for cognitive rehabilitation.
Introduction

There is a growing body of evidence suggesting that patients with brain injury may perform appropriately on standard tests of executive functioning, yet at the same time face significant difficulties in organizing and executing everyday tasks (Shallice and Burgess, 1991; Bennett, Ong and Ponsford, 2005; Alderman and Baker, 2009). To explain this discrepancy, it has been argued that standard executive tests provide useful results with regard to the executive strengths and weaknesses of patients with acquired brain injury, but that they do not sufficiently represent real-world demands and are less suited to predict the nature and severity of executive deficits of patients in their everyday life. Still, little research has been done on the relation between executive test scores and executive functioning in real-life (Wilson et al., 2009).

To overcome this problem, more ecologically valid executive tests, such as the Behavioural Assessment of Dysexecutive Syndrome (BADS) (Wilson et al., 1996), have been developed. These tests are aimed at improving the assessment of real-life executive functioning. In addition to these tests, observation rating scales, such as the Dysexecutive Questionnaire (DEX) (Wilson et al., 1996) included in the BDAS executive battery, have also been designed to assess post-injury behavioural changes in daily executive functioning. These new measures may provide clinicians with more accurate and reliable information about the daily executive problems of their patients and can be useful in assessing the effectiveness of treatments targeted at executive functioning in daily life (Wilson et al., 2009).

In several studies the DEX has been applied to investigate the ecological validity of the BADS. Typically, the DEX-rating scales of informants were usually completed by family members of patients with chronic brain injury (Norris and Tate, 2000). The majority of the studies have shown that the DEX is associated more strongly with the BADS than with other standard executive tests, with the DEX- reports of family members stronger related to the BADS performance than the DEX- self- reports of the patients (Wilson et al., 1996; Burgess et al., 1998; Sbordone et al., 1998). These findings are attributed to the lack of insight and to the poor self- awareness of the patients, making the DEX- ratings of family members more accurate and reliable (Wilson et al., 1996; Burgess et al., 1998; Sbordone et al., 1998).

Several studies, however, have questioned the applicability of the DEX-reports of family members as an estimator of executive dysfunction (Bennett et al., 2005; Channon and Crawford, 1999; Knight et al., 2002). Some studies have shown that the DEX- reports of family members are less sensitive to executive dysfunction, as low or no significant correlations were found between the DEX- reports of family members and BADS subtests (Evans et al., 1997; Norris and Tate, 2000). Other studies have shown that family members do not adequately identify problems reported by other, more independent raters (Riccio et al., 1994). In addition, the DEX- reportings of
family members could not distinguish brain damaged patients from healthy controls (Channon and Crawford, 1999). Moreover, the DEX does not specify a time and spatial frame within which estimations about the patient’s behaviour should be made, and consequently family members may be less accurate in detecting daily dysexecutive symptoms, especially in an acute rehabilitation setting (Bennett et al., 2005).

The Bennett et al. study (2005) included DEX-self reports and DEX-reports of family members, but also DEX-reports of clinical neuropsychologists and occupational therapists (DEX-reports of therapists, DEX-TH). Their results showed that the DEX-reports of the patients and those of their family members were less accurate at identifying executive dysfunction as measured by the BADS than those completed by therapists (DEX-TH). Apparently, the daily contact of the therapists with the patients resulted in a better knowledge of everyday executive difficulties. Bennett et al. (2005) also suggest that future research should investigate the sensitivity of the DEX to identify differences in dysexecutive behaviours related to the location of brain damage. Previous studies recruited patients of mixed-etiology brain damage in the chronic stage and healthy controls to investigate the ecological validity of the BADS and other executive tests (Chan and Manly, 2002; Bogod et al., 2003; Hart et al., 2005). Some of these studies also investigated clinical populations with behavioural symptoms attributable to frontal dysfunction, including patients with schizophrenia (Evans et al., 1997), frontotemporal dementia (Ziauddeen and Murray, 2010) and multiple sclerosis (Norris and Tate, 2000). No studies exist that examined DEX in patients who have localized brain injuries, taking lesion location into account. The first goal of the present study was to investigate the validity of the DEX-self reports of patients with brain injury and the DEX-reports of their therapists (DEX-TH) to identify differences in the presence and severity level of daily dysexecutive problems according to the location of the brain damage: anterior lesions (AL) and posterior lesions (PL).

Our second goal was to examine the strength of associations between the DEX rating scale and the BADS total score as well as other real-life executive tests, such as the Everyday Description Task (EDT) (Dritschel et al., 1998) and the Twenty Question Test (TQT) (Laine and Butters, 1982). While previous work has established a strong association between the DEX-rating scale of informants and the performance of the patients on the BADS (Wilson et al., 1996; Burgess et al., 1998; Bennett et al., 2005), the validity of the DEX to adequately identify daily life executive problems measured by other executive tasks has not been investigated so far. In daily life, executive impairments are most visible in open-ended and unstructured tasks. Therefore, to validate the DEX, two test tasks that are genuinely open-ended and loosely organized were chosen, e.g. the EDT and TQT. Moreover, an additional goal was to explore the relation between the DEX and six BADS subtests which were
sensitive and specific indicators of anterior pathology (Emmanouel et al., 2014). Several previous lesion and neuroimaging studies have indicated the involvement of both anterior and posterior brain regions in executive test performance. Impairments on executive tests may be attributed to posterior lesions, albeit to a significantly lesser degree than anterior damage (Zalonis et al., 2009; Emmanouel et al., 2014). The results of our previous study (Emmanouel et al., 2014), for example, indicate that deficits measured by several BADS subtests, sensitive to anterior pathology, may be partially explained by posterior lesions, suggesting an engagement of these regions in the more “content-specific” aspects of these multifactorial executive tasks rather than in their ‘central’ executive characteristics.

Our last goal in the present research work was to investigate the contribution of these ‘anterior’ executive measures to the prediction of daily dysexecutive symptoms of the patients as recorded in the DEX-TH reporting scales.

**Methods**

**Participants**

Fifty two patients and 29 healthy controls participated in this study. Forty one patients were in treatment at the ‘Anagennisi’ Rehabilitation Center in Nea Rebestos, Thessaloniki, Greece. The other eleven were recruited from the neurosurgery department of the Saint Lukas Clinic in Panorama, Thessaloniki, Greece. The female/male ratio for the patients groups was 28/22, whereas it was 18/11 for the controls.

**Inclusion Criteria**

All patients included in this study had documented brain injury with AL or PL, verified on CT and/or MRI-scans. Thirty patients had AL (frontal/fronto-temporal cortical or anterior subcortical), whereas 22 patients had focal PL (parietal/occipital cortical). Table 1 shows the distribution of the patient groups according to the lesion location, its aetiology and the side of the brain damage.

All patients were at least 6 months post-onset when assessment took place (time since injury ranged from 6 to 46 months, $M = 11.5$ months, $SD = 8.508$). Traumatically injured patients and patients with a haemorrhagic stroke had experienced a loss of consciousness following brain damage and the duration of coma ranged from 7 to 24 days (coma duration, $M = 15.83$, $SD = 4.99$). All patients (TBI, stroke, tumour) participating in this study were inpatients with severe motor and sensory impairments at the time of onset (TBI, stroke) or after surgery (tumours). These sensorimotor deficits required clinical physiotherapy for at least three months. Additional medical information was available for 11 stroke patients: 8 with PL had a history of uncontrolled hypertension and 3 (1 AL and 2 PL) had a history of a trial fibrillation. Among the
post-surgery tumour patients, 9 (4 AL and 5 with PL) had a history of persistent epilepsy, whereas 8 (5 AL and 3 PL) had suffered a sudden seizure with loss of consciousness prior to surgery.

Besides the lesion location criterion, all patients with brain injury selected for this study were signalled by their therapists (mostly physiotherapists and speech-therapists) for having executive difficulties in their everyday activities and during therapeutic sessions. Subsequently, the same therapists were asked to observe these problems using the Greek translation of Spikman’s Checklist of Executive Disorders (Spikman, 2002). This checklist consists of 2 parts, a cognitive part and a section with social and awareness questions. The nine cognitive items ask about difficulties in daily life with working memory (in particular mental manipulation of information), attention (like distractibility and divided attention), planning and execution, decision making and reasoning, abstraction, problem-solving, flexibility, initiative and insight. Three items assess the presence of social problems like

<table>
<thead>
<tr>
<th>Lesion Location</th>
<th>Etiology</th>
<th>Hemisphere-sided</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anterior:</strong> frontal/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>frontal-temporal damage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cortical or subcortical)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Number of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total: 30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Trauma (predominantly prefrontal damage)</td>
<td>6 LH 7 RH</td>
</tr>
<tr>
<td>8</td>
<td>Stroke</td>
<td>3 LH haemorrhagic (basal ganglia) 2 RH haemorrhagic (basal ganglia) 3 RH ischemic</td>
</tr>
<tr>
<td>9</td>
<td>Lobectomy (tumour surgery)</td>
<td>3 LH 6 RH</td>
</tr>
<tr>
<td><strong>Posterior:</strong> parietal/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>parietal-occipital damage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total: 22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Trauma</td>
<td>1 LH, 3 RH</td>
</tr>
<tr>
<td>10</td>
<td>Stroke</td>
<td>1 LH ischemic 2 RH haemorrhagic 7 RH ischemic</td>
</tr>
<tr>
<td>8</td>
<td>Lobectomy (tumour surgery)</td>
<td>5 LH 3 RH</td>
</tr>
</tbody>
</table>

Table 1 Lesion location and etiology within the patient groups.
relational difficulties, problems at work, and troubles with social contacts and leisure. Two separate questions evaluate the awareness of executive problems of patient and of proxies. Every item can be answered with yes (problem present) or no. The therapists were familiar with the patients, having worked with them for several months. The procedure was blind, as therapists in Greece are mainly occupied with the functional consequences of brain damage and they are only marginally interested in information about lesion location.

**Exclusion criteria**

Patients with progressive neurological disease, severe behavioural disorders, severe verbal, sexual or aggressive disinhibition, severe loss of initiative (abulia), lack of awareness of deficit (anosognosia), severe aphasia, severe hemi-inattention, previous psychiatric disorders and substance abuse, were excluded from the study. The exclusion of patients with severe behavioural problems was mostly related to their difficulties in cooperating with the examiner, the lack of involvement in the assessment process and the inability to complete the tasks used in the present study. None of our patients had visual-field defects that interfered with the administration of the tests as verified in their medical records. Patients were also excluded if they had severe memory problems. Memory and language measures were also used in the selection of the patients (see Emmanouel et al., 2014, for details on the memory and language variables). A control group of 29 healthy adults (HCs) was recruited via relatives of the patients and the researcher’s environment. None of the HCs had a history of neurologic or psychiatric disease (self-report).

Mean Scores and SD, as well as statistical tests for demographic data and IQ are presented in table 2. No significant group differences were found among the three participant groups with respect to age (ranging from 18-61 years), educational level (ranging from 9-17 years), handedness as assessed with the Annett Hand Preference Questionnaire (Annett and Klishaw, 1983) or general intellectual ability based on the participants’ performance on Raven’s Standard Progressive Matrices.

**Materials**

**Standard Executive Tests**

All the patients and the 29 HCs underwent an assessment of their executive deficits using seven standard executive measures, sensitive indicators of AL (Stuss and Levine, 2002; Bennett et al., 2005; Alvarez and Emory, 2006). The seven standard executive measures included in this study were used as screening tools of executive dysfunction and derived from the standard version of the WCST (Heaton, 1981), a Greek version of the Stroop Word Colour Test (Zalonis et al., 2009), a Greek version of the Verbal Fluency Test (Kosmidis, 2004), a Greek version of the Trail Making Test (Zalonis et al., 2008) and the Digit Span Backward subtest from the Wechsler Adult
Intelligence Scale-III (WAIS-III; Wechsler, 1997). These tests yielded the following variables: 1) WCST number of correct categories – WCSTCat, 2) number of WCST perseveration errors – WCSTPersev., 3) WCST ratio of perseveration errors compared to the total trials completed – WCSTPersev/tot, 4) Stroop Word Colour Interference condition – StroopInterf., 5) ratio of Phonemic Fluency Score (total number of correct words generated) compared to Semantic Fluency Score – VFP/S, 6) Trail Making Test ratio of time to complete part B compared to the time to complete part A (TMT B/A) and 7) Digit Span Backward (DigitB). The Mean Scores and SD as well as significant group differences among the three participant groups in these seven standard executive variables are presented in table 3.

**Dysexecutive Questionnaire (DEX)**

In order to investigate the first goal of this study, the 20-item DEX-Questionnaire, translated into Greek, was used to evaluate complaints of post-injury daily behavioural changes of patients with brain injury during their everyday routines in clinical and rehabilitation settings. The 20-item DEX was designed to estimate four areas of change: emotional or personality changes, motivational changes, behavioural and cognitive changes (Wilson et al., 1996). Each item is scored on a 5-point Likert scale ranging from ‘never’ to ‘very often’. The scores on each item are suggested to indicate the severity level of the daily executive problems experienced by patients with brain injury (Wilson, 1996; Bennett et al., 2005).

Both patients with AL and PL completed the DEX-self reporting scale. Furthermore, the same sample of professional therapists interviewed with the Checklist of Executive
Disorders (Spikman, 2002), subsequently completed the DEX-rating scale of informants (DEX-reporting scale of therapists, DEX-TH). The dependent variable was the 20-item total raw score of the DEX, indicative of the severity of the dysexecutive symptoms in everyday lives of the patients.
The DEX-self-report and the DEX-rating scales of informants were also administered to the healthy control group and their relatives respectively and were used as control measures in order to establish the appropriateness of the DEX to detect brain damage.

**Behavioural Assessment of Dysexecutive Syndrome (BADS)**
To investigate the second goal of the present study, all participants completed the BADS (Wilson et al., 1996). For research purposes all the BADS subtests instructions and materials were translated into Greek. The BADS executive variables included in this study were the total raw score of the BADS executive battery (BADS) and the raw scores on the BADS subtests found to be sensitive and specific indicators of AL in our previous research work (Emmanouel et al., 2014). Notably, our previous results indicated the raw scores of the Rule Shifting subtest, the Action Program subtest, the Key Search subtest and the Zoo Map subtest as sensitive indicators of AL executive dysfunction. Moreover, the Modified Six Elements subtest and the Zoo Map Test Condition 2 were found to be specific to AL (Emmanouel et al., 2014). The Temporal Judgment subtest (and the Zoo Map Condition 1) was not included in the present study as our previous findings indicated that these BADS subtests were neither sensitive (nor specific) to anterior lesions.

**Twenty Questions Test (TQT)**
The TQT is a conceptual problem solving task requiring the participants to guess which of 42 drawings of objects representing overlapping classes, such as animals, clothing, or round objects, the examiner has in mind. To this end, the participants can ask questions to which the examiner can only answer ‘Yes’ or ‘No’. A maximum of twenty questions is allowed before the test is ended. The executive measure derived from this test was the total number of questions asked (TQT) by the participants. Difficulties in this problem solving domain are primarily associated with frontal lobe dysfunction (Lezak, 1995; Upton and Thomson, 1999).

**Everyday Description Task (EDT)**
The EDT (Dritschel et al., 1998) is a script generation task that consists of eight questions requiring the participants to describe how they would perform activities of daily living. Each of these activities represents a set of familiar actions and sequential ordering of these actions is asked. The total number of relevant actions generated by the participants in the correct order (EDT) was scored. According to Grafman’s theory (Grafman 1989; 1994) the term script refers to managerial knowledge units (MKUs) that consist of goal-oriented sets of overlearned daily life actions, structured in hierarchical sequential order and stored in prefrontal brain areas (Godbout et al., 2005; Allain et al., 2012). Deficits in script generation tasks are indicative of executive
dysfunction, but recent studies have shown that these deficits are not exclusively related to prefrontal pathology (Godbout et al., 2005; Boelen et al., 2011; Allain et al., 2012).

### Table 4

Mean raw Scores (+ SD), results of Mann-Whitney U tests (two-tailed) post-hoc multiple comparisons between the HCs and patients with AL, between HCs and patients with PL and between the two patient groups after statistically significant Kruskal-Wallis differences in the BADS, EDT and TQT executive variables, Bonferroni adjustment $\alpha=0.017$.

<table>
<thead>
<tr>
<th>Test</th>
<th>AL M (SD) (N = 30)</th>
<th>PL M (SD) (N = 22)</th>
<th>HCs M (SD) (N = 29)</th>
<th>$\chi^2$ and $p$</th>
<th>Post-hoc Comparisons*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BADS</td>
<td>34.7 (6.3)</td>
<td>37.3 (6.15)</td>
<td>44.1 (2.24)</td>
<td>$\chi^2(2) = 36.9$</td>
<td>a, b, c</td>
</tr>
<tr>
<td>Rule Shifting</td>
<td>4.00 (3.08)</td>
<td>1.40 (1.76)</td>
<td>0.10 (0.40)</td>
<td>$\chi^2(2) = 40.69$</td>
<td>a, b, c</td>
</tr>
<tr>
<td>Action Program</td>
<td>3.2 (0.96)</td>
<td>4.18 (0.79)</td>
<td>4.68 (0.47)</td>
<td>$\chi^2(2) = 34.34$</td>
<td>a, b, c</td>
</tr>
<tr>
<td>Key Search</td>
<td>8.8 (261)</td>
<td>11.09 (3.44)</td>
<td>14.17 (1.3)</td>
<td>$\chi^2(2) = 38.61$</td>
<td>a, b, c</td>
</tr>
<tr>
<td>Zoo Map 2</td>
<td>6.7 (1.6)</td>
<td>7.63 (1.13)</td>
<td>7.96 (0.18)</td>
<td>$\chi^2(2) = 25.87$</td>
<td>a, c</td>
</tr>
<tr>
<td>Zoo Map</td>
<td>10.46 (3.15)</td>
<td>12.77 (3.08)</td>
<td>15.37 (0.90)</td>
<td>$\chi^2(2) = 39.15$</td>
<td>a, b, c</td>
</tr>
<tr>
<td>Modified Six Elements Test</td>
<td>4.00 (0.98)</td>
<td>5.40 (0.85)</td>
<td>5.86 (0.85)</td>
<td>$\chi^2(2) = 45.623$</td>
<td>a, c</td>
</tr>
<tr>
<td>EDT</td>
<td>35.03 (9.046)</td>
<td>48.14 (12.826)</td>
<td>60.10 (6.444)</td>
<td>$\chi^2(2) = 45.679$</td>
<td>a, b, c</td>
</tr>
<tr>
<td>TQT</td>
<td>16.10 (4.589)</td>
<td>12.86 (4.902)</td>
<td>8.48 (2.707)</td>
<td>$\chi^2(2) = 29.765$</td>
<td>a, b, c</td>
</tr>
</tbody>
</table>

AL: patients with anterior lesions, PL: posteriorly lesioned patients, HCs: Healthy Controls.

*a, significant difference: HCs better than AL (all $z > -3.137$, all $p < 0.002$, $r = 0.34 - 0.69$); b, significant difference: HCs better than PL (all $z > -2.539$, all $p < 0.011$, $r = 0.28 - 0.39$); c, significant difference: AL worse than PL (all $z > -2.431$, all $p < 0.015$, $r = 0.30 - 0.49$).


Procedure
All the patients underwent four or more testing sessions. The total time to complete all of the executive measures took approximately five hours. All the questionnaires and tests were also administered to the HCs in two testing sessions, each lasting approximately 2 hours. The administration order of all the measures was the same so for all groups (firstly the standard executive, memory and language tests in approximately two sessions, next the BADS executive battery along with the DEX-Questionnaire in one session, and finally the EDT and the TQT in one more session).

All the patients in this study had been inpatients at the rehabilitation center ‘Anagennisi’ and in the clinical frame of Saint Loukas Clinic, Thessaloniki, Greece for a long period of time, ranging from at least 6 months to 30 months post-injury and were well known to their therapists. Before completing the DEX-self reporting scale, the patients were given detailed instructions on how to report the presence and severity of their daily dysexecutive behaviours. Their physiotherapists and speech-therapists were asked to complete the DEX-TH reporting scales as informants. The blind procedure previously applied using the Checklist of the Executive Disorders was also followed with the DEX.

Statistical analyses
Prior to the statistical analysis of the data, the distributions of the scores on behavioural (the DEX-self and the DEX- rating scales of informants) and real-life executive measures (the BADS, EDT and TQT variables) were explored using the Shapiro-Wilk’s normality tests. All these executive variables were found to be skewed. Therefore, they were transformed and tested again for normality. Negatively skewed variables were transformed using square transformation ($x^2$), whereas for positively skewed square root transformation was used (Clark-Carter, 2010). All these executive variables were found non-normally distributed and stayed so after transformation.

In order to establish the validity of the DEX to distinguish brain – injured patients from HCs, non-parametric independent sample Mann-Whitney U-tests (one-tailed) were conducted in order to investigate the differences in the total scores on the DEX-self reports between the patients as a whole group and the HCs. Mann-Whitney tests were also computed to examine the differences in the scores of the DEX-TH and the DEX-healthy relatives’ reports. With regard to the first aim of our study, non-parametric Kruskal-Wallis tests were used to examine whether there were significant differences in the DEX-self reports as well as in the DEX- reports of informants among the three participant groups, i.e. the patient group with AL, the group with PL and the HCs.

To investigate the validity of the DEX – self reports of the patients and the DEX-TH reports to identify differences in the severity of the daily dysexecutive symptoms
according to the lesion location, further multiple post-hoc comparisons were conducted using two-tailed Mann-Whitney U tests among the three participant groups (patients with AL, patients with PL, HCs). Bonferroni correction (α set at 0.017) was used to control for Type 1 errors across pair-wise tests. Effect sizes were computed for non-parametric post-hoc Mann-Whitney comparisons using an approximate value of $r$. This $r$ value was calculated by dividing the value of $z$ in the Mann-Whitney test by the square root of $N$ (Cohen, 1988). The effect sizes were interpreted according to Cohen’s (1988) criteria (0.1 = small, 0.3 = medium, 0.5 = large). Additional non-parametric spearman $\rho$ correlations were computed between the DEX-self reports of the patients with AL and the DEX-self reports of the patients with PL. The same analyses were conducted between the DEX-self reports of the patients with AL and their DEX-TH reports as well as between the DEX-self reports of the patients with PL and their DEX-TH reports. The squared $\rho$ coefficients $\rho^2$ were also used as effect sizes (Cohen, 1988).

With regard to our second goal, non-parametric Spearman $\rho$ correlations were computed to investigate whether the DEX-self reports of the patients were associated with the BADS, the EDT and the TQT. The same analyses were conducted between the DEX-TH reports and the above mentioned executive measures. Correlations were also computed between the DEX-self reports and the BADS subtests found to be sensitive and specific indicators of AL (Emmanouel et al., 2014). The same analyses were performed to examine the association between the DEX-TH reports and the above BADS subtests. Effect sizes were also calculated.

Finally, a standard multiple regression analysis was conducted in order to investigate the contribution of each of the real-life variables (BADS, the EDT and TQT), to predict the total scores on the DEX-TH rating scales. The BADS, the EDT and the TQT were entered in the model as the potential predictors of the total DEX-scores of the therapists. Effect sizes using Cohen’s $f^2$ and were also calculated. The same analysis was computed to investigate the contribution of each of the BADS subtests that were sensitive indicators of AL, to the DEX-TH reporting scales.

**Results**

Table 5 shows the means and SD of the DEX-self reporting and DEX-reporting scales of informants of the three participant groups. Statistical comparisons revealed that the total raw scores on the DEX-self reporting scales of the HCs were significantly lower than those of the patients with AL ($n$ = 59, $z$ = - 6.050, $p < 0.0005$, $r = - 0.78$) and of the patients with PL ($n$ = 51, $z$ = - 5.349, $p < 0.0005$, $r = - 0.74$). As expected, both patients with AL and patients with PL reported significantly more severe daily dysexecutive problems than the HCs. On the other hand, the total raw scores on the
DEX HC’s relatives’ reports were significantly lower than those of the DEX –Therapists reports (DEX-TH), in both the patients with AL (n = 59, z = - 6.583, p < 0.0005, r= - 0.85) and the patients with PL (n = 51, z = - 5.538, p < 0.0005, r = - 0.77). The therapists of both patients groups reported significantly more severe everyday dysexecutive symptoms in everyday lives of their patients than the relatives of HCs.

More importantly, the patient group with AL and the patients with PL differed significantly on the total raw scores of the DEX-TH reporting scales, whereas no significant differences between these groups were found on the DEX-self reports. Specifically, the DEX-TH total raw scores of the patient group with AL were significantly higher than the DEX-TH total raw scores of the group with PL (n = 52, z = - 4.449, p < 0.0005, r= - 0.61). This means that the therapists of the patients with AL observed significantly more severe executive difficulties in everyday lives of their patients than the therapists of the patients with PL. However, no significant differences were found between the DEX self-reports of the patients with AL and the DEX-self reports of the patients with PL (n = 52, z = - 0.279, p > 0.017).

Moreover, non-parametric Spearman correlations showed a significant positive correlation between the DEX-self reports of the patients with PL and the DEX-reports of their therapists (ρ = 0.670, p = 0.001, effect size ρ² = 0.44), indicating relatively good awareness of executive difficulties in this patient group. On the contrary, no
significant correlations were found between the DEX-self reports of the patients with AL and their DEX-TH reports \((r = -0.073, p = 0.7)\).

Table 6 shows the non-parametric Spearman correlations between the DEX-self reports of the patients and their performances on the BADS, the EDT and the TQT, as well as the correlations between the DEX-TH reporting scales and the same real-life executive variables (along with the \(\rho^2\) effect sizes).

<table>
<thead>
<tr>
<th></th>
<th>DEX-Self (N = 52)</th>
<th>DEX-TH (N = 52)</th>
<th>effect size (\rho^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BADS</td>
<td>0.072</td>
<td>-0.555**</td>
<td>0.30</td>
</tr>
<tr>
<td>Rule Shifting</td>
<td>0.075</td>
<td>0.507**</td>
<td>0.26</td>
</tr>
<tr>
<td>Action Program</td>
<td>-0.298*</td>
<td>-0.500**</td>
<td>0.25</td>
</tr>
<tr>
<td>Key Search</td>
<td>0.052</td>
<td>-0.496**</td>
<td>0.24</td>
</tr>
<tr>
<td>Zoo Map test</td>
<td>0.039</td>
<td>-0.508**</td>
<td>0.26</td>
</tr>
<tr>
<td>Zoo Map 2</td>
<td>-0.086</td>
<td>-0.505**</td>
<td>0.26</td>
</tr>
<tr>
<td>Modified Six</td>
<td>0.044</td>
<td>-0.661**</td>
<td>0.43</td>
</tr>
<tr>
<td>Elements Test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TQT</td>
<td>-0.129</td>
<td>0.411**</td>
<td>0.2</td>
</tr>
<tr>
<td>EDT</td>
<td>-0.225</td>
<td>-0.497**</td>
<td>0.24</td>
</tr>
</tbody>
</table>

* Correlation significant at the 0.05 level (two-tailed), ** Correlation significant at the 0.01 level (2-tailed).

The total raw scores on the DEX-TH reporting scales were significantly correlated with the performance of the patients on the BADS, the EDT and the TQT, all indicators of AL. In other words, the higher the total scores on the DEX-TH reporting scales, the lower the performances of their patients on these three executive tests. The DEX-TH rating scales were correlated as strongly with the EDT and the TQT almost as with the BADS. However, no significant correlations were found between the total raw scores on the DEX-self reports of the patients and the same measures of executive dysfunction. Additionally, significant negative correlations were found between the total raw scores on the DEX-TH rating scales and all BADS indicators of AL (see table 5). On the other hand, no significant associations were found between the total raw scores on the DEX-self reporting scales of the patients and the same executive measures except for a moderate correlation with the Action Program subtest.
Finally, the results of the multiple regression analysis are illustrated in table 7.

Table 7 Results of the multiple regression analyses using the BADS, the EDT, the TQT and the BADS subtests as predictors of the total DEX-TH scores.

<table>
<thead>
<tr>
<th>Executive Measures</th>
<th>( \beta )</th>
<th>( t )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>BADS</td>
<td>-0.379</td>
<td>-2.771</td>
<td>0.008*</td>
</tr>
<tr>
<td>TQT</td>
<td>0.188</td>
<td>1.342</td>
<td>0.186</td>
</tr>
<tr>
<td>EDT</td>
<td>-0.165</td>
<td>-1.043</td>
<td>0.302</td>
</tr>
<tr>
<td>Rule Shifting</td>
<td>0.008</td>
<td>0.052</td>
<td>0.959</td>
</tr>
<tr>
<td>Action Program</td>
<td>-0.176</td>
<td>-1.169</td>
<td>0.249</td>
</tr>
<tr>
<td>Key Search</td>
<td>-0.239</td>
<td>-1.547</td>
<td>0.129</td>
</tr>
<tr>
<td>Zoo Map Test</td>
<td>0.314</td>
<td>1.349</td>
<td>0.184</td>
</tr>
<tr>
<td>Zoo Map 2</td>
<td>-0.235</td>
<td>-1.201</td>
<td>0.236</td>
</tr>
<tr>
<td>Modified Six Elements Test</td>
<td>-0.496</td>
<td>-2.825</td>
<td>0.007*</td>
</tr>
</tbody>
</table>

The full model containing the BADS, the EDT and the TQT as predictors was statistically significant \([\text{Adjusted } R^2 = 0.304, F = (3.48) = 8.432, p < 0.0005, \text{effect size Cohen’s } f^2 = 0.436]\), but only the BADS made a unique contribution to the prediction of the DEX-TH ratings \((\beta = -0.379, p = 0.008)\). Additional analysis of the contribution of each of the BADS indicators of AL to the DEX-TH ratings revealed that the whole model was statistically significant \([\text{Adjusted } R^2 = 0.413, F = (6, 45) = 6.971, p < 0.0005, \text{effect size Cohen’s } f^2 = 0.7]\), but only the Modified Six Elements Test was a unique predictor of the DEX-TH ratings, contributing to 49.6% of the variance on the total DEX- scores of therapists \((\beta = -0.496, p = 0.007)\).
Discussion

Our first goal was to investigate the validity of the DEX-self reportings and the DEX-reportings of informants in relation to anterior brain pathology. The results of the present study show no significant differences between the DEX-self reports of the patients with AL and the DEX-self reports of the patients with PL. However, significant differences were found between the DEX-TH reports of the group with AL and the DEX-TH reports of the group with PL, with more severe executive problems reported by the therapists of the group with AL. This indicates the inability of the patients with AL to provide reliable information about their daily dysexecutive symptoms, whereas their therapists can accurately identify them. Thus, the DEX-TH rating scale is highly accurate and sensitive when assessing the severity of daily dysexecutive behaviours of patients with AL. This result is strengthened further by our correlation analyses. While the DEX-self reports of the patients with PL were positively correlated with their DEX-TH reports, no significant correlations were found between the DEX-self reports of the patients with AL and their DEX-TH reports. This is in agreement with the results of previous studies, which explain this discrepancy by referring to the poor insight and lack of self-awareness of dysexecutive patients (Wilson et al., 1996; Burgess et al., 1998; Norris and Tate, 2000; Bennett et al., 2005; Hart et al., 2005; Bivona et al., 2008). Additionally, our study clearly emphasizes that this interpretation mainly applies to patients with anterior pathology.

As expected, our findings indicate that the DEX-TH rating scale can accurately distinguish patients with brain injury from healthy controls. More importantly, our findings reveal that the DEX-TH ratings adequately detect more severe daily dysexecutive problems in the patients with AL than in those with PL who are receiving rehabilitation at least six months post-injury. Our results are in line with Bennett et al.’s (2005) findings with regard to the applicability of the DEX as a screening instrument for acute rehabilitation settings, provided that it is completed by professional personnel trained to be sensitive to the cognitive and behavioural aspects of the dysexecutive syndrome. Furthermore, our research extends Bennett et al. (2005) since we show that the DEX-TH rating scale can appropriately discriminate anteriorly lesioned patients from patients with posterior damage.

Our findings seem in contrast with Boelen et al. (2009) who did not find significant group differences between the DEX-reports of the patients, family members and therapists in their sample. This could be attributed to the fact that the patients in that study were outpatients who had less intensive therapy contacts than the inpatients in our and Bennett et al. studies (2005). This may have resulted in less informed DEX-TH reports. Our findings emphasize that the environmental frame in which therapeutic observations are made is crucial when using the DEX-rating scale of informants or similar behavioural measures of executive dysfunctioning. DEX-TH ratings in
combination with the performance of the patients with AL on executive function tests may provide clinicians with relevant information to refine diagnostic conclusions and tailor consequent rehabilitation.

Our second goal was to investigate associations between the DEX-self rating scales and three real-life executive test measures indicative of anterior brain pathology, that is, the BADS, EDT and TQT. The same correlations were calculated with respect to the DEX-TH rating scales. Significant negative correlations were only found between the DEX-TH reporting scales and these three real-life executive variables. More specifically, more severe dysexecutive behaviour reported on the DEX-TH was associated with worse performances on these three executive measures. These associations of the DEX-TH with the EDT, the TQT and the BADS were almost equally strong. This suggests that, like the BADS, the EDT and the TQT can be appropriately used as ecologically valid measures of executive dysfunction. We found the same significant associations between the DEX-TH and the six BADS subtests, sensitive and specific indicators of anterior pathology. The strongest of these associations was between the DEX-TH and the Modified Six Elements Test.

The present study also revealed that from the three real-life executive tasks only the BADS significantly contributed to the DEX-TH score. From the BADS subtests that were previously identified as being sensitive to anterior pathology (Emmanouel et al., 2014) only the Modified Six Elements Test significantly predicted the DEX-TH ratings. This is in line with Bennett et al. (2005), who showed that the Modified Six Elements Test, as well as the Action Program subtest were found to be predictive of the everyday executive difficulties of the patients as reported by professional personnel using the DEX. The results from the correlation and regression analyses of the present study and Bennett et al. (2005) suggest that the Modified Six Elements Test is almost as sensitive as the whole BADS battery to daily dysexecutive symptoms of patients with brain injury as reported in the DEX-TH. These findings may have important implications for a more accurate, yet less time-consuming neuropsychological assessment of patients with severe and prominent daily dysexecutive symptoms. The Modified Six Elements Test combined with the DEX-TH may potentially provide a brief screening for patients with severe executive problems. The Modified Six Elements Test is an open-ended and ill-structured planning task requiring intentionality, inhibition (Burgess et al., 1998; Andres, 2003), the use of working memory and rule switching within time constraints. These executive cognitive processes are also required in many everyday executive demands. Also, rehabilitation interventions have been developed that provide compensatory strategies for exactly these executive processes, such as Problem Solving Therapy and Goal Management Training (Levine et al., 2000; Spikman et al., 2010; Simblett and Bateman, 2011), the use of errorless learning strategies (Kessels and De Haan, 2003; Bertens et al., 2013), adaptive coping techniques (Anson and Ponsford, 2006) or Time Pressure Management
(Fasotti et al., 2000). These treatment approaches seem more appropriate for such impairments than drill-and-practice treatments for these everyday dysexecutive behaviours.

In conclusion, the DEX-TH is strongly correlated with the BADS - Modified Six Elements Test, measuring executive functioning in open-ended activities of daily living relying on multiple executive processes. Consequently, therapists of dysexecutive patients after brain damage can provide accurate and reliable information about the severity level of daily executive difficulties of their patients using the DEX in clinical and rehabilitation settings. This applies to observations made in long-term intensive settings, where therapists know their patients well, rather than in other shorter-term or outpatient settings. This aspect is needed to be taken into consideration when using the DEX-Questionnaire or similar behavioural measures of executive dysfunctioning.
References


Evans, J. J., Chua, S. E., McKenna, P. J., & Wilson, B. A. (1997). Assessment of the dysexecutive syndrome in schizophrenia. Psychological Medicine, 27, 635–646.


Script generation and executive dysfunction in patients with anterior and posterior brain lesions

Abstract

Introduction: Studies on script processing have shown inconsistent relations between deficits in script action generation and frontal lobe pathology. Therefore, we investigated which difficulties in script action generation are linked to anterior lesions. Moreover, we explored whether verbal script generation can be predicted by specific executive processes.

Methods: Fifty-two patients with acquired brain injury (mean age: 44.23 years, 30 male/22 female) were included, of whom 30 had anterior and 22 posterior lesions. Several indices of the Everyday Description Task were investigated: relevant central actions (RCAs); relevant trivial actions (RTAs); relevant and irrelevant intrusions (RI & IRI); sequencing (SEs) and perseverative (PEs) errors. Additionally, five z-composite scores representing planning, response generation, working memory, inhibition and shifting were calculated. Correlations and multiple linear regression analyses were computed.

Results: Anteriorly-lesioned patients produced significantly less RCAs and more PEs and SEs compared to posteriorly-damaged patients. No differences were found with RTAs, RI and IRI. RCAs were predicted by planning, response generation and working memory, RI by response generation and working memory, IRI by inhibition, PEs and SEs by response generation and shifting. None of these executive processes predicted RTAs.

Conclusions: Difficulties in RCAs, PEs and SEs are sensitive indicators of anterior brain damage and script generation demands various executive abilities.

Key words: script generation, brain injury, anterior pathology, executive dysfunction, multistep activities of daily living.
Introduction

Difficulties in performing goal-directed activities of daily living (ADL) after acquired brain injury have been interpreted as an impairment in activating action knowledge units of experienced events from semantic memory, referred to as scripts (Allain et al., 2011; 2012; Boelen et al., 2011). According to Wood and Grafman (2003), scripts are managerial knowledge units stored as structured event complexes in the frontal lobes. Scripts contain a semantic dimension, including (1) central and/or distinctive actions which are essential in a script, (i.e; ‘Ask for the menu’ which can only be found in the script ‘Going to a restaurant’) and (2) trivial actions, that can be part of the script, but are not necessary and specific to the script (i.e: ‘Take off coat’ which can be found in several scripts: ‘Going to a restaurant’ or ‘Going to the movies’ scripts).

Within a script, actions are structured following a sequential order, with a clear beginning and an end (Allain et al., 2011; 2012; Boelen, 2011). Wood and Grafman (2003) also suggest that both the semantic- and the sequential dimensions of a script are stored and activated within the prefrontal regions. Thus, damage in these areas may negatively affect script generation and, as a consequence, everyday action planning.

In order to verify Grafman’s predictions, several studies (Chevignard et al., 2000 Fortin et al., 2003; Godbout et al., 2004; Zanini, 2008; Allain, 2011; 2012) have compared patients with frontal lobe damage to patients with posterior lesions and/or healthy controls in verbal script generation and script sequencing tasks.

Studies investigating the relation between the production of correct actions and frontal pathology have yielded mixed results. Godbout et al. (2004) and Chevignard et al. (2000) found that patients with frontal lesions produced significantly less correct actions in comparison with patients with posterior lesions and healthy controls. However, other investigations have shown that patients with frontal lesions produced similar numbers of correct actions compared to healthy controls (Cazalis et al., 2001; Zanini et al., 2002; Fortin et al, 2003; Godbout et al., 2005; Allain et al., 2011; 2012). On the other hand, patients with frontal damage have consistently been found to produce more sequencing errors (i.e. errors in organizing actions in the correct temporal order) and perseverative errors (i.e. actions repetition) in both script generation (Fortin et al., 2003; Godbout et al., 2004; Zanini, 2008) and script sequencing tasks (Zalla et al., 1998; Allain et al, 2001; Zanini et al., 2002). In summary, the above mentioned studies showed a consistent relation of anterior pathology with deficits in script sequencing, but not with the total number of correct actions produced in verbal script generation.

These conflicting results can be attributed to several factors, among which the use of different types of multistep activities, the number of actions included in the scripts, the presence or absence of headers, the degree of the familiarity of the
required actions and the low power of the majority of the studies. In the Cazalis et al. study (2001), for example, there were differences between patients with TBI and healthy controls in the number of actions produced in novel and non-routine tasks, but these differences did not reach significance because the study was underpowered, with only 12 patients and 12 controls. On the contrary, Chevignard et al. (2000), Fortin et al. (2003) and Godbout et al. (2004) used a larger number of script tasks, each including numerous actions. These studies showed a significantly poorer action generation in TBI patients compared to posteriorly lesioned patients and healthy controls.

Furthermore, in some of these studies patient groups with other lesions were used (Cazalis et al., 2001; Allain et al., 2012) and only a few included patients with well-selected anterior lesions (e.g. Zanini et al., 2002). The patients included in the study of Cazalis et al. (2001), for instance, suffered diffuse axonal injury without any focal cortical damage. On the contrary, patients in the studies of Chevignard et al. (2000), Fortin et al. (2003) and Godbout et al. (2004) had focal cortical lesions, which may explain their more extensive deficits. However, even with well-selected patients, the latter studies were also underpowered due to small study samples. For example, Fortin et al. (2003) used only 9 frontal and 1 dubious (only «suspected» frontal damaged) patient. Similarly, only a few patients with well-selected anterior lesions were included in the Godbout et al. study (2005). In the Zanini et al. study (2008) in which the highest number of anteriorly damaged patients (9) was compared to 9 healthy controls, a mean difference of about twelve generated actions between the two groups (p>.09) in favour of healthy controls was found in novel and non-routine scripts. Here also, no significant differences were found, seemingly due to the small samples investigated.

Thus, former studies were generally underpowered, including either small number of well-selected patients with focal frontal damage or mixed groups with diffuse injuries or groups with more extensive damage, e.g. patients with Huntington disease in the Allain et al. study, (2012). Therefore, we have tried to select a substantial number of patients with verified anterior lesions (30 patients). The main goal of the present study was to examine whether there is a relation between script generation and anterior damage. For this purpose, we studied (verbal) script generation in 30 patients with focal anterior lesions, 22 patients with lesions in the posterior regions and 29 healthy controls. We also verified that patients included in our study had executive difficulties in everyday life. The verbal script tasks that we used were all derived from the Everyday Description Task (EDT; Dritschel et al., 1998). The EDT includes eight open, free-response script tasks in which the participants have to describe how they would perform activities of daily living. Each of these activities represents a set of familiar actions-steps and the sequential ordering of these actions is asked. We expected our patients with focal brain damage to show more difficulties
in generating verbal scripts compared to healthy controls and that patients with anterior lesions would produce significantly less correct actions than patients with posterior lesions. Deficits in verbal script generation may indicate difficulties in action planning and therefore contribute to an accurate detection and management of such impairments in patients with brain damage. Additionally, the script tasks used in the present study were assessed with a well-investigated scoring method (Boelen et al., 2011; Allain et al., 2011) aimed at identifying different kinds of relevant and irrelevant actions (and errors).

Moreover, only a limited number of studies have explored the relation between scores on executive tests and script generation performance (Godbout et al., 2005; McWilliams and Schmitter-Edgecombe, 2008; Allain et al., 2011; Boelen et al., 2011). These studies have revealed significant correlations between: 1) errors on the Trail Making Test, the Modified Card Sorting Test, the Stroop Test and sequencing errors (Allain et al., 2011), 2) poor performances on the category fluency task (representing semantic memory deficits) and sequencing errors (McWilliams and Schmitter-Edgecombe, 2008; Allain et al., 2011), 3) global executive test performance and script execution (e.g. preparing a meal) (Godbout et al., 2005), and 4) global executive test performance and total error score (sequencing and perseverative errors, and irrelevant intrusions) in verbal script generation tasks (the Everyday Description Task; Dritschel et al., 1998; Boelen et al., 2011). Thus, our second goal was more explorative, i.e. to determine the specific executive processes that predict performance in script tasks. Our hypothesis was that successful performance in script generation tasks would demand the integration of multiple aspects of executive functioning.

Methods

Participants
Fifty two patients took part in this study. Forty one were in treatment at the ‘Anagennisi’ Rehabilitation Centre in Nea Redestos, Thessaloniki, Greece and 11 were recruited from the neurosurgery department of the Saint Lukas Clinic in Panorama, Thessaloniki, Greece. All these patients and the 29 healthy control subjects included in this study had already participated in one of our previous studies (Emmanouel et al., 2014).

Patient selection criteria
All patients (30 male/ 22 female) had documented brain injuries verified by CT and/or MRI-scans. Thirty patients with anterior lesions were included in our study, of whom the majority (13) had suffered traumatic brain injury with identified cerebral contusions and subdural haemorrhage. These patients had primary frontal dysfunctions, also including a disconnection of the prefrontal regions from other anterior cortical or
subcortical areas or combined damage to these anterior brain areas (fronto-temporal cortical or anterior subcortical damage). The rest of the patients included in this group were 8 patients with stroke and 9 patients with a history of surgically resected anterior tumours. Twenty two patients with focal posterior lesions (parietal/occipital cortical damage mainly due to stroke and focal tumours after lobectomy) were also selected to participate in this study. All patients were at least 6 months post-onset when assessment took place (time since injury ranged from 6–46 months, \( M = 11.5 \) months, SD = 8.508). Table 1 shows the distribution of the patient groups according to lesion location and aetiology.

<table>
<thead>
<tr>
<th>Lesion Location</th>
<th>Aetiology</th>
<th>Hemisphere-sided</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AL:</strong> frontal/frontal-temporal damage (cortical or subcortical)</td>
<td>(Left-sided: LH; Right-sided: RH)</td>
<td></td>
</tr>
<tr>
<td>(Number of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total: 30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Trauma (predominantly prefrontal damage)</td>
<td>6 LH 7 RH</td>
</tr>
<tr>
<td>8</td>
<td>Stroke</td>
<td>3 LH haemorrhagic (basal ganglia) 2 RH haemorrhagic (basal ganglia) 3 RH ischemic</td>
</tr>
<tr>
<td>9</td>
<td>Lobectomy (tumour surgery)</td>
<td>3 LH 6 RH</td>
</tr>
<tr>
<td><strong>PL:</strong> parietal/parietal-occipital damage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total: 22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Trauma</td>
<td>1 LH, 3 RH</td>
</tr>
<tr>
<td>10</td>
<td>Stroke</td>
<td>1 LH ischemic 2 RH haemorrhagic 7 RH ischemic</td>
</tr>
<tr>
<td>8</td>
<td>Lobectomy (tumour surgery)</td>
<td>5 LH 3 RH</td>
</tr>
</tbody>
</table>

Beside the lesion location criterion, all patients with anterior and posterior lesions had executive difficulties in everyday life and during therapy sessions, as ascertained by their therapists (physiotherapists and speech-therapists), using a Greek translation of Spikman’s Checklist of Executive Disorders (Spikman, 2002). This Checklist is a
structured interview, screening several cognitive, awareness and psychosocial executive problems in real-life situations.

**Exclusion criteria**

Patients with neurodegenerative disorders, severe psychiatric problems, severe verbal, sexual or aggressive disinhibition, severe abulia and anosognosia (lack of awareness of deficit), severe aphasia, severe hemi-inattention and a history of substance abuse were excluded from the study. Patients were also excluded if they had severe learning difficulties and long-term memory problems.

Mean Scores and SDs, as well as statistical tests for demographic data and IQ are presented in table 2. No significant group differences were found between patients with anterior lesions, patients with posterior lesions and healthy controls with respect to age (ranging from 18-61 years), educational level (ranging from 9-17 years) or general intellectual ability, based on the participants’ performances on Raven’s Standard Progressive Matrices. Also, the same groups’ performances did not differ in a set of memory and language tests (for details of these measures, see Emmanouel et al., 2014).

**Table 2** Mean Scores (+SD), results of parametric one-way ANOVAs (one-tailed) for variables of group differences in demographic data and estimated I.Q. for patients with anterior lesions (N = 30), patients with posterior lesions (N = 22) and Healthy Controls (N = 29).

<table>
<thead>
<tr>
<th>Variable</th>
<th>AL M (SD)</th>
<th>PL M (SD)</th>
<th>HCs M (SD)</th>
<th>df</th>
<th>F and p (1-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41.47 (15.40)</td>
<td>48 (10.73)</td>
<td>41.72 (13.02)</td>
<td>2</td>
<td>F = 1.82, p = .16</td>
</tr>
<tr>
<td>Education</td>
<td>12.97 (2.07)</td>
<td>12.50 (2.11)</td>
<td>13.10 (2.22)</td>
<td>2</td>
<td>F = .52, p = .59</td>
</tr>
<tr>
<td>PM (IQ)</td>
<td>103.53 (6.46)</td>
<td>105.86 (5.22)</td>
<td>106.62 (6.65)</td>
<td>2</td>
<td>F = 1.95, p = .15</td>
</tr>
</tbody>
</table>

AL: patients with AL lesions, PL: PL lesioned patients, HCs: Healthy Controls.

**Assessment of executive function**

Executive functions were assessed using twelve executive test variables, previously found to be sensitive to anterior brain damage (Wilson et al., 1996; Stuss et al., 1998, 2000, 2001; Stuss & Alexander, 2000; Stuss and Levine, 2002; Alvarez & Emory, 2006, Emmanouel et al., 2014). A therapist’s version of the DEX-Questionnaire
(DEX-TH; Wilson et al., 1996) was also administered. Among these executive measures (see Table 3 for details), the Stroop Interference score was calculated as the ratio of the total number of coloured stimuli named in Condition III (colour hues printed as competing colour words, within 45 seconds) to the colours named in Condition II (colour hues printed as XXX, also within 45 seconds), in a fixed order for all the three Stroop conditions, according to Golden’s (1978) scoring method (Golden, 2000). With respect to the Verbal Fluency Test, a Greek version was used (Kosmidis et al., 2004). Table 3 also shows the means and SD’s of the executive variables, along with the results of post-hoc multiple (pair-wise) comparisons (following one-way ANOVAs and Kruskal-Wallis tests).

**Table 3** Mean raw Scores (+ SD) results of Mann-Whitney U tests (two-tailed) post-hoc multiple comparisons between the HCs and the patients with AL, between HCs and the patients with PL and between the two patient groups after statistically significant Kruskal-Wallis differences in the executive variables, Bonferroni adjustment $\alpha=0.017$.

<table>
<thead>
<tr>
<th>Variable</th>
<th>AL (M, SD)</th>
<th>PL (M, SD)</th>
<th>HCs (M, SD)</th>
<th>$\chi^2$ and p (1-tailed)</th>
<th>Post-hoc comparisons 1 2 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEX-TH</td>
<td>24.20 (11.81)</td>
<td>9.73 (6.67)</td>
<td>0.90 (0.11)</td>
<td>$\chi^2 (2) = 59.56$ p &lt; .0005</td>
<td>1 2 3</td>
</tr>
<tr>
<td>DigitB</td>
<td>6.63 (1.24)</td>
<td>7.95 (1.67)</td>
<td>8.2 (1.67)</td>
<td>$\chi^2 (2) = 14.82$ p = .001</td>
<td>1 3</td>
</tr>
<tr>
<td>TMTB/A</td>
<td>3.11 (1.24)</td>
<td>2.25 (0.71)</td>
<td>1.92 (0.54)</td>
<td>$\chi^2 (2) = 23.56$ p = .0005</td>
<td>1 3</td>
</tr>
<tr>
<td>StroopInterf.</td>
<td>-6.68 (6.83)</td>
<td>-2.1 (4.13)</td>
<td>3 (2.65)</td>
<td>$\chi^2 (2) = 3.06$ p = .0005</td>
<td>1 2</td>
</tr>
<tr>
<td>WCSTCat.</td>
<td>2.56 (1.67)</td>
<td>4.81 (1.56)</td>
<td>5.96 (0.18)</td>
<td>$\chi^2 (2) = 48.18$ p = .0005</td>
<td>1 2 3</td>
</tr>
<tr>
<td>WCSTPersev.</td>
<td>67.1 (25.00)</td>
<td>32.68 (24.95)</td>
<td>13.41 (9.77)</td>
<td>$\chi^2 (2) = 44.38$ p = .0005</td>
<td>1 2 3</td>
</tr>
<tr>
<td>VF Semantic</td>
<td>42.97 (9.88)</td>
<td>50.27 (8.55)</td>
<td>60.21 (7.84)</td>
<td>$\chi^2 (2) = 37.09$ p = .005</td>
<td>1 2 3</td>
</tr>
<tr>
<td>VF Phonemic</td>
<td>18.47 (8.38)</td>
<td>27.45 (8.92)</td>
<td>41.28 (7.14)</td>
<td>$\chi^2 (2) = 49.45$ p = .001</td>
<td>1 2 3</td>
</tr>
<tr>
<td>BADSRule</td>
<td>4.00 (3.08)</td>
<td>1.40 (1.76)</td>
<td>0.10 (0.40)</td>
<td>$\chi^2 (2) = 40.69$ p = .0005</td>
<td>1 2 3</td>
</tr>
</tbody>
</table>
Procedure

All the executive tests were administered by the clinical neuropsychologist-examiner of this study, in three or more 4-hour assessment sessions and in a fixed order of administration i.e. first Spikman’s Executive Checklist and then the executive tests and the DEX-TH followed by the Greek translation of the Everyday Description Task (EDT; Dritschel et al., 1998).

Measures

Everyday Description Task (EDT)

The EDT is a free-response verbal script generation task that consists of eight questions, requiring participants to tell how they would perform activities of daily living (see table 4). Participants were asked to verbally express the sequence of actions corresponding to each activity in the correct order. The eight activities were
presented in the same order to all subjects. The participants were not prompted to continue when they stopped. Subjects’ responses were audiotaped, then written out and scored.

**EDT Scoring**
All the responses of the 29 healthy controls on the eight scripts were scored based on the criteria established by Boelen et al. (2011) and Allain et al. (2011). The first step in scoring the actions generated by the healthy control group was to establish a script corpus, i.e. a standard list of sequential actions for each script, expressing agreement about the actions named by healthy subjects. The inclusion of an action in the script corpus was based on a pre-set criterion percentage of minimally 18% of healthy controls mentioning the action. Next, actions were classified as major steps if they were mentioned by at least 60% of the healthy controls, minor steps if they were mentioned by 40-59% of the healthy controls, or trivial steps if they were mentioned by 18-39% of the healthy controls. Thus, major actions were considered to be the most central features to the theme or goal of each of the scripts (e.g. ‘booking / making a reservation’ in the ‘take a trip with friends’ script). Minor actions were considered to be less critical than major actions, but still representative script features of the target activity, (e.g. ‘booking rooms/tickets through internet’ or ‘call/go to a travel agency to arrange everything’ in the ‘take a trip with friends’ script). Major and minor actions together constituted the relevant central actions of a script. Trivial actions were relevant script features estimated to be peripheral to (but still a part of) the target activity (e.g. ‘Take into consideration the weather conditions in order to organize the trip’ in the ‘take a trip with friends’ script). Evoked actions that did not reach the minimal frequency of 18% were characterized as intrusions. Relevant

<table>
<thead>
<tr>
<th>Table 4</th>
<th>The eight scripts of the Everyday Description Task.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Purchase a household appliance</td>
<td></td>
</tr>
<tr>
<td>2) Take a trip with friends</td>
<td></td>
</tr>
<tr>
<td>3) Get a new job</td>
<td></td>
</tr>
<tr>
<td>4) Organize a move</td>
<td></td>
</tr>
<tr>
<td>5) Do the washing up</td>
<td></td>
</tr>
<tr>
<td>6) Put on a shirt</td>
<td></td>
</tr>
<tr>
<td>7) Paint a room</td>
<td></td>
</tr>
<tr>
<td>8) Make a sand castle</td>
<td></td>
</tr>
</tbody>
</table>


intrusions were part of a script (e.g. ‘Use a ladder to reach the wall and paint it’ in the ‘paint a room’ script). Irrelevant intrusions (IRI) did not belong to the script (e.g. “choose a colour that matches with the colours of other rooms’ in the ‘paint a room’ script) and were scored as errors. Moreover, perseverations i.e. actions repeated within the same script, and sequencing errors, i.e. errors in the logical sequence of the script, e.g. booking hotel rooms without firstly selecting the exact place/time /date in the ‘take a trip with friends’ script were also scored as errors.
Composite Executive Function Variables

Five z-composite executive function variables were created based on the z-values of individual executive test measures. Lesion and factor-analytic studies have shown that these composite variables represent five basic executive (sub) domains (Miyake et al., 2000; Stuss et al., 2001; Stuss and Levine, 2002; Bennett et al., 2005; Alvarez and Emory, 2006; Espinosa et al., 2009; Oosterman et al., 2012; 2013). Before grouping, z-scores with negative valence were reversed, so that higher z-composite scores all represented better performance. Table 5 illustrates the five composite executive domains investigated in this study and their component test variables.

Statistical analyses

First, all the data derived from the six EDT variables, i.e. the relevant central actions of a script (RCA), the relevant trivial actions (RTA), the relevant intrusions (RI) and irrelevant intrusions (IRI) as well as the perseverations (PE) and sequencing errors (SE) were tested for normality with Shapiro-Wilk’s tests. All the EDT variables were found to be skewed, except for the RCA. All the skewed variables were transformed using square transformation ($x^2$), whereas for positively skewed variables a square root transformation was used (Clark-Carter, 1997). Even after transformation all these variables remained skewed.

Due to the relatively high number of TBI patients (n=13) in the group with anterior lesions in comparison with the posterior lesion group (n = 4), we performed subgroup analyses on the six EDT variables. For this purpose, parametric t-tests (for the normally distributed RCA) and non-parametric Mann-Whitney U-tests were computed to compare the TBI subgroup with the other patients (n = 13 vs n = 17) within the group with anterior brain damage.

Afterwards, with respect to our first goal, parametric one-way ANOVAs (for the normally distributed RCA variable) and non-parametric Kruskal-Wallis tests (for the rest of the EDT variables) were used, to examine whether there were significant differences in EDT scores among the three participant groups. To investigate which of the six EDT measures discriminated between-group differences (i.e. patients with anterior lesions vs. healthy controls, patients with posterior lesions vs. healthy controls, and patients with anterior lesions vs. patients with posterior lesions), further multiple post-hoc comparisons were conducted using parametric two-tailed Dunnett’s t-test (after significant one-way ANOVAs, $p < .01$) and two-tailed Mann-Whitney U tests (after significant Kruskal-Wallis differences, $p < .01$). Bonferroni correction (set at .017) was used to control for Type 1 errors across pair-wise comparisons. Effect sizes were computed for parametric Dunnett’s t-test using $\eta^2_p$ and non-parametric post-hoc Mann-Whitney comparisons using an approximate value of $r$. This $r$ value was calculated by dividing the value of $z$ in the Mann-Whitney test by the square root of $n$ (Field, 2005). The effect sizes were estimated according
to Cohen’s (1988) criteria (0.1 = small, 0.3 = medium, 0.5 = large). Our aim was to investigate which EDT variables were sensitive to brain damage and successively which EDT variables were indicative for anterior pathology. Therefore, stepwise regression analyses with the two patient groups were carried out. To explore which of the EDT measures would predict group membership (anterior versus posterior damage) we used the Forward Selection: LR method with entry testing based on the significance of the score statistic.

With regard to our second goal, six non-parametric Spearman ρ correlations (level of significance ρ = .01) were calculated for each of the six EDT variables expressed in z-values and the five z-composite executive test variables representing ‘Planning’, ‘Response generation’, ‘Working Memory’, ‘Inhibition’ and ‘Shifting’). The z-values of the EDT variables with negative valence (i.e. the RI and IRI, PE and SE), were reversed for the correlation analyses, so that all scores were in the same direction (with higher scores representing better performance). P-value (set at .00167) and effect sizes (ρ²) were also adjusted.

Finally, multiple linear regression analyses were conducted in order to investigate the impact of the five executive domains on each of the six EDT measures. In these analyses the z-composite executive variables were entered as potential predictors (independent variables) of each EDT variable. In this case the significance value (ρ = .05) was adjusted and set at .008 (.05/6 = .008).

Results

The subgroup comparisons between patients with TBI and patients with other aetiologies within the anterior group revealed no differences in performance on the six EDT variables [for the RCA, t (28) = .78, p = .43; for the other five EDT variables, all z scores < 1.96, all p scores > .05]. Table 6 shows the results of the One-Way ANOVA and Kruskal-Wallis tests used to investigate differences among the three participant groups (i.e. patients with anterior lesions vs. patients with posterior lesions vs. healthy controls) in each of the six EDT variables, i.e. the relevant central actions of a script (RCA), the relevant trivial actions (RTA), the relevant intrusions (RI) and irrelevant intrusions (IRI) as well as the perseverations (PE) and sequencing errors (SE). The results revealed significant differences among the three groups on all the EDT variables, except for the RTA (see Table 6). Further parametric post-hoc multiple comparisons, using Dunnett’s two-sided t-tests, were conducted, to compare healthy controls and patients with anterior lesions, healthy controls and patients with posterior lesions and the two patient groups for total number of RCA produced. These analyses showed that the total number of RCA generated in the healthy control group was significantly higher than in the group with anterior lesions (n=59, mean difference =
18.41, \( p < .001, \eta^2_p = .8 \) and in the group with posterior lesions \( (n = 51, \text{mean difference} = -10.29, p < .001, \eta^2_p = -.56) \). Patients with posterior lesions were also found to produce a significantly higher number of RCA compared to the group of patients with anterior lesions \( (n = 52, \text{mean difference} = 8.12, p < .001, \eta^2_p = .48) \).

Additional non-parametric post-hoc multiple comparisons using two-tailed Mann-Whitney U tests showed that, as anticipated, healthy controls generated

Table 6 Mean raw Scores (+ SD), results of parametric Dunnett’s t-tests and non-parametric Mann-Whitney U tests (two-tailed) post-hoc multiple comparisons between the HCs and the patients with AL, between HCs and the patients with PL and between the two patient groups after statistically significant One-Way ANOVA and Kruskal-Wallis differences in the EDT variables. Bonferroni adjustment \( \alpha = 0.017 \).

<table>
<thead>
<tr>
<th>Variables</th>
<th>AL M (SD)</th>
<th>PL M (SD)</th>
<th>HCs M (SD)</th>
<th>df</th>
<th>( F ) and ( p ) (1-tailed)</th>
<th>Post-hoc comparisons 1 2 3 (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>39.83 (6.57)</td>
<td>47.95 (8.08)</td>
<td>58.25 (6.85)</td>
<td>(2,80)</td>
<td>( F = 38.63 )</td>
<td>1 2 3</td>
</tr>
<tr>
<td>RTA</td>
<td>2.10 (1.49)</td>
<td>2.14 (1.24)</td>
<td>1.97 (1.80)</td>
<td>( \chi^2 (2) = 0.42 )</td>
<td>p = .81</td>
<td></td>
</tr>
<tr>
<td>RI</td>
<td>1.80 (1.62)</td>
<td>1.41 (1.18)</td>
<td>0.17 (0.38)</td>
<td>( \chi^2 (2) = 0.22 )</td>
<td>p = .00*</td>
<td></td>
</tr>
<tr>
<td>IRI</td>
<td>7.77 (2.72)</td>
<td>5.59 (2.97)</td>
<td>1.48 (0.82)</td>
<td>( \chi^2 (2) = 10.73 )</td>
<td>1 2</td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>2.47 (1.33)</td>
<td>1.55 (1.29)</td>
<td>0.28 (0.44)</td>
<td>( \chi^2 (2) = 35.29 )</td>
<td>1 2 3</td>
<td></td>
</tr>
<tr>
<td>SE</td>
<td>5.00 (1.64)</td>
<td>3.64 (2.06)</td>
<td>1.17 (0.75)</td>
<td>( \chi^2 (2) = 48.65 )</td>
<td>1 2 3</td>
<td></td>
</tr>
</tbody>
</table>

RCA: the total number of the Relevant Central (major + minor) Actions produced in the EDT script generation task; RTA: the total number of the EDT Relevant Trivial actions; RI: the total number of the EDT Relevant Intrusions; IRI: the total number of the EDT Irrelevant Intrusions; PE: the total number of the Perseverative errors committed in the EDT script descriptions; SE: the total number of the Sequencing errors committed in the EDT script descriptions.

* statistical significance
1 HCs significantly better than AL \( (\text{all z} > -2.96, \text{all } p < .013, \text{effect sizes } r = .48 - .73) \).
2 HCs significantly better than PL \( (\text{all z} > -3.23, \text{all } p < .001, \text{r = .44 – .53}) \).
3 AL significantly worse than PL \( (\text{all z} > -2.36, \text{all } p < .017, r = .27, .28 \text{ respectively}) \).
significantly less total RI and IRI and committed significantly less PE and SE than both patients with anterior lesions and patients with posterior lesions (see bottom of table 6). Multiple Mann-Whitney pair-wise comparisons between the two patient groups also revealed that patients with anterior lesions committed significantly more PE and SE than patients with posterior lesions (also bottom of table 6), whereas no significant differences were found between the two patient groups in the total production of RI ($z = - .82, p = .41$) and the total production of IRI ($z = - .50, p = .61$).

To further investigate which of the three EDT measures (RCA, PE and SE) could predict group membership (anterior or posterior damage), a stepwise logistic regression analysis (forward: LR method) was conducted. The results of this regression analysis are presented in Table 7. The model was statistically significant at step 1 $\chi^2 (1, 52) = 13.86, p < .001$. Only RCA had a significant impact on the dependent variable ‘lesion location’. The probability of the Wald statistic for RCA was significant (see table 7) and this variable discriminated patients with anterior lesions and those with posterior lesions with an accuracy of 67.3%.

With respect to the second goal of our study, the results of six separate non-parametric Spearman $\rho$ correlation analyses (adjusted $\alpha = .00167$, and $\rho^2$ effect sizes) are presented in table 8. Significant positive correlations were found between the $z$-total number of RCA and all the $z$-composite executive domains (all $\rho > .51$, all $p < .00167$, effect sizes $\rho^2 = .26 – .65$). These correlations indicate that the better the performances in the executive domains of ‘Planning’, ‘Response generation’, ‘Working Memory’, ‘Inhibition’ and ‘Shifting’, the higher the total number of RCA generated in EDT scripts.

<table>
<thead>
<tr>
<th>Step 1</th>
<th>$\beta$</th>
<th>S.E</th>
<th>Wald</th>
<th>df</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables in the Equation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDT RCA</td>
<td>-0.152</td>
<td>0.048</td>
<td>9.86</td>
<td>1,52</td>
<td>.002*</td>
</tr>
<tr>
<td>Constant</td>
<td>6.931</td>
<td>2.132</td>
<td>10.56</td>
<td>1,52</td>
<td>.001</td>
</tr>
<tr>
<td>Step 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variables not in the Equation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDT PE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.16</td>
</tr>
<tr>
<td>EDT SE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.57</td>
</tr>
</tbody>
</table>

* statistical significance
However, no significant correlations were found between the total number of RTA and these five executive domains (all $p > .27$). On the other hand, significant positive correlations were found between RI and scores in the domains of ‘Planning’ ($p = .001$), ‘and Productivity ($p = .00$) (all significant $s > .27$, effect sizes $\rho^2 = .08 - .3$). Significant positive correlations were also found between the score of the IRI and the composite measures of ‘Inhibition’, ‘Response generation’ and ‘Planning’ (all

### Table 8

Six Spearman $\rho$ correlations between the six EDT script generation performances and the z-composite scores of the five basic executive domains.

<table>
<thead>
<tr>
<th>EDT Relevant Executive Domains</th>
<th>RCA (effect size $\rho^2$)</th>
<th>RTA (effect size $\rho^2$)</th>
<th>RI (effect size $\rho^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning</td>
<td>.80** (.65)</td>
<td>-.06 (.12)</td>
<td>.36** (.27)</td>
</tr>
<tr>
<td>Response generation</td>
<td>.77** (.60)</td>
<td>.01 (.30)</td>
<td>.52** (.37)</td>
</tr>
<tr>
<td>Working Memory</td>
<td>.70** (.49)</td>
<td>.12 (.15)</td>
<td>.15 (.15)</td>
</tr>
<tr>
<td>Inhibition</td>
<td>.53** (.28)</td>
<td>.07 (.09)</td>
<td>.29 (.29)</td>
</tr>
<tr>
<td>Shifting</td>
<td>.51** (.26)</td>
<td>-.08 (.09)</td>
<td>.27 (.27)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EDT Errors</th>
<th>IRI (effect size $\rho^2$)</th>
<th>PE (effect size $\rho^2$)</th>
<th>SE (effect size $\rho^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning</td>
<td>.26* (.07)</td>
<td>.59** (.35)</td>
<td>.63** (.40)</td>
</tr>
<tr>
<td>Response generation</td>
<td>.31** (.10)</td>
<td>.61** (.37)</td>
<td>.67** (.45)</td>
</tr>
<tr>
<td>Working Memory</td>
<td>.18 (.18)</td>
<td>.41** (.20)</td>
<td>.44** (.20)</td>
</tr>
<tr>
<td>Inhibition</td>
<td>.38** (.01)</td>
<td>.32** (.10)</td>
<td>.48** (.23)</td>
</tr>
<tr>
<td>Shifting</td>
<td>.12 (.28)</td>
<td>.53** (.29)</td>
<td>.53** (.29)</td>
</tr>
</tbody>
</table>

** Correlation significant at $\alpha$ adjusted level $(.01/6) = .00167$(2-tailed).
significant $p > .27$, all $p < .00$, effect sizes $\rho^2 = .07 - .15$). Similarly, significant positive correlations were seen between the scores of PE and all executive domains (all significant $p$ scores $> .32$, all $p$ scores $= .00$, effect sizes $\rho^2 = .10 - .37$) and the SE (all significant $p$ scores $> .44$, all $p$ scores $< .00$, effect sizes $\rho^2 = .2 - .45$) committed in the EDT scripts.

Table 9  Results of the multiple regression analyses using the five basic executive domains as predictors of each of the EDT measures (expressed in $z$ values).

<table>
<thead>
<tr>
<th>EDT Relevant Executive Domains</th>
<th>RCA ($\beta$ and $p$)</th>
<th>RTA ($\beta$ and $p$)</th>
<th>RI ($\beta$ and $p$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning</td>
<td>$\beta = .38$</td>
<td>$\beta = -.09$</td>
<td>$\beta = .05$</td>
</tr>
<tr>
<td></td>
<td>$p = .00^*$</td>
<td>$p = .60$</td>
<td>$p = .75$</td>
</tr>
<tr>
<td>Response generation</td>
<td>$\beta = .29$</td>
<td>$\beta = -.04$</td>
<td>$\beta = .59$</td>
</tr>
<tr>
<td></td>
<td>$p = .003^*$</td>
<td>$p = .82$</td>
<td>$p = .00^*$</td>
</tr>
<tr>
<td>Working Memory</td>
<td>$\beta = .29$</td>
<td>$\beta = .16$</td>
<td>$\beta = -.34$</td>
</tr>
<tr>
<td></td>
<td>$p = .002^*$</td>
<td>$p = .31$</td>
<td>$p = .01$</td>
</tr>
<tr>
<td>Inhibition</td>
<td>$\beta = .013$</td>
<td>$\beta = .08$</td>
<td>$\beta = .13$</td>
</tr>
<tr>
<td></td>
<td>$p = .86$</td>
<td>$p = .54$</td>
<td>$p = .28$</td>
</tr>
<tr>
<td>Shifting</td>
<td>$\beta = .02$</td>
<td>$\beta = -.02$</td>
<td>$\beta = .10$</td>
</tr>
<tr>
<td></td>
<td>$p = .38$</td>
<td>$p = .90$</td>
<td>$p = .39$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EDT Errors</th>
<th>IRI ($\beta$ and $p$)</th>
<th>PE ($\beta$ and $p$)</th>
<th>SE ($\beta$ and $p$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning</td>
<td>$\beta = -.07$</td>
<td>$\beta = .23$</td>
<td>$\beta = .17$</td>
</tr>
<tr>
<td></td>
<td>$p = .67$</td>
<td>$p = .08$</td>
<td>$p = .19$</td>
</tr>
<tr>
<td>Response generation</td>
<td>$\beta = .21$</td>
<td>$\beta = .41$</td>
<td>$\beta = .44$</td>
</tr>
<tr>
<td></td>
<td>$p = .20$</td>
<td>$p = .002^*$</td>
<td>$p = .001^*$</td>
</tr>
<tr>
<td>Working Memory</td>
<td>$\beta = .01$</td>
<td>$\beta = -.08$</td>
<td>$\beta = -.92$</td>
</tr>
<tr>
<td></td>
<td>$p = .92$</td>
<td>$p = .48$</td>
<td>$p = .36$</td>
</tr>
<tr>
<td>Inhibition</td>
<td>$\beta = .27$</td>
<td>$\beta = -.31$</td>
<td>$\beta = .02$</td>
</tr>
<tr>
<td></td>
<td>$p = .03$</td>
<td>$p = .18$</td>
<td>$p = .98$</td>
</tr>
<tr>
<td>Shifting</td>
<td>$\beta = -.02$</td>
<td>$\beta = .26$</td>
<td>$\beta = .29$</td>
</tr>
<tr>
<td></td>
<td>$p = .86$</td>
<td>$p = .017$</td>
<td>$p = .008^*$</td>
</tr>
</tbody>
</table>

* statistical significance at $\alpha$ adjusted level ($0.05/6$) $= .008$ (two-tailed).
Finally, six separate multiple regression analyses were performed, including each of the six EDT scores as dependent variables and the five executive domains as predictors. The results of these analyses (p-values set at .008) are summarized in Table 9.

The first model, including RCA as a dependent variable, was statistically significant, as the five -composite executive variables were found to explain 70.7% of the variability of RCA \(\text{Adjusted } R^2 = .68, F = (5, 75) = 36.22, p < .001\), effect size Cohen's \(f^2 = 2.20\). Additional analysis (with an adjusted p-value = .008) revealed that ‘Working Memory’ (\(\beta = .29, p = .002\)), ‘Planning’ (\(\beta = .38, p = .00\)) and ‘Response generation’ (\(\beta = .29, p = .003\)) contributed significantly to the prediction of the total number of RCA in the EDT scripts. The second model with RTA as dependent variable was not statistically significant \(\text{Adjusted } R^2 = -.041, F = (5, 75) = .37, p = .86\), indicating that none of the five executive domains can significantly predict RTA. The next analysis including RI as a dependent measure, was statistically significant \(\text{Adjusted } R^2 = .29, F = (5, 75) = 7.61, p < .001\), effect size Cohen's \(f^2 = .41\), indicating ‘Response generation’ (\(\beta = .59, p < .001\)) as the major predictor of RI, that accounted for 33.7% of the variance of RI. The fourth model, using IRI as dependent variable, was not significant \(\text{Adjusted } R^2 = .073, F = (5, 75) = .13, p = .057\), effect size Cohen's \(f^2 = .08\). The next analysis, with PE as dependent variable, was statistically significant \(\text{Adjusted } R^2 = .45, F = (5, 75) = 14.40, p < .001\), effect size Cohen's \(f^2 = .82\), revealing ‘Response generation’ as the predictor of PE accounting for 48.65% of PE variance. Finally, the sixth model, with SE as a dependent variable, was statistically significant, predicting 50.95 % of SE variance \(\text{Adjusted } R^2 = .47, F = (5, 75) = 15.52, p < .001\), effect size Cohen's \(f^2 = .90\) and disclosing ‘Response generation’ (\(\beta = 0.44, p < .001\)) and ‘Shifting’ (\(\beta = 0.29, p = .008\)) as significant predictors of SE.

**Discussion**

The first goal of this study was to investigate whether there were differences in verbal script action generation according to location of brain pathology (anterior vs. posterior damage). Therefore, we compared the performance of 3 groups (healthy controls, patients with posterior lesions and patients with anterior lesions) on six relevant script action variables.

Before proceeding with these comparisons, we conducted subgroup analyses comparing patients with TBI and patients with other aetiologies within the anterior group on these six script variables. This was done due to the higher proportion of people with TBI (n = 13) in the anterior group as compared to the posterior group (n = 4). No significant differences were found between patients with TBI and patients with other aetiologies within the anterior group. This finding indicated that the
performances were affected by ‘anterior’ brain damage, regardless of its aetiology. However, the higher proportion of patients with TBI in the anterior group as compared with those included in the posterior group is a limitation of our study (and other relevant studies) and an issue that should be taken into consideration in future studies.

The comparisons among the three participant groups showed that patients with anterior lesions generated significantly less relevant central actions (RCA) than both the group of patients with posterior lesions and the healthy control group. This finding suggests that the generation of RCAs is likely to be impaired after anterior brain damage. This conclusion was also drawn from our regression analyses, which indicated that RCAs were the only significant predictor of anterior dysfunction. So, a deficiency or a loss of ‘centrality’ in the core of actions needed for the accurate organization and generation of a script can be interpreted as a dysfunction primarily related to anterior pathology. The higher number of omissions made by patients with anterior lesions in the production of correct script actions can be explained as a form of ‘goal neglect’, due to dissociation between the main activity and the list of actions that needs to be generated to achieve this activity (Duncan et al., 1996).

On the other hand, no significant differences were found among patients with anterior lesions, patients with posterior lesions and healthy controls in the generation of relevant trivial actions (RTA), which are actions of low frequency (mentioned by 18-39 % of the healthy controls). This means that, on the one hand, the production of high-frequency actions central to a script (i.e. RCA) is significantly affected by brain damage and especially by anterior pathology, but on the other hand, the production of RTA (i.e. low-frequency actions) remains relatively intact after brain damage. This strengthens the conclusion of former studies (Sirigu et al., 1995; Boelen et al., 2011), those patients with frontal damage and executive deficits have prominent difficulties in generating the central actions of a script.

Our findings also show that the two patient groups did not differ in their total production of relevant (RI) and irrelevant intrusions (IRI) in script generation, whereas both patient groups generated significantly more intrusions than the healthy control group. These results imply that difficulties in inhibiting relevant and irrelevant intrusions in script generation pertain to brain damage but cannot be exclusively attributed to anterior pathology. They can be better interpreted as a dysfunction within a broader neural network involving both the frontal lobes and other, more posterior, regions. These findings are in agreement with several other studies (Boelen et al., 2011; Zalla et al., 1998; Godbout and Doyon, 2000).

Our study also revealed differences between the three participant groups in the total number of perseverative (PE) and sequencing errors (SE). Healthy controls produced significantly less PE and SE than both patients with posterior and anterior lesions, whereas patients with anterior lesions generated significantly more PE and SE than those with posterior lesions. This indicates that patients with anterior lesions
have more difficulties in sequencing steps in logical order during action production. The production of perseverative and sequencing errors by these patients may also be indicative for working memory problems, like retaining the correct string of actions while generating a script. On the other hand, the number of RI and IRI that interfered with the correct description of the scripts were not found sensitive to anterior brain damage. The finding that patients with anterior lesions committed significantly more PE and SE within the EDT scripts is in accordance with previous studies, revealing a strong relationship between the production of SE and PE within script generation tasks and frontal executive dysfunction (Fortin et al., 2003; Godbout et al., 2004; Zanini, 2008; Allain et al., 2011).

Taken together, and in line with Chevignard et al. (2000), our results show that difficulties in RCA, PE and SE are sensitive indicators of anterior brain damage. Patients with posterior lesions may also be impaired in these script parameters, but to a significantly lesser degree than patients with anterior damage. Thus, these indices can be useful for the assessment of the executive problems that patients with anterior brain damage (e.g. patients with TBI) face in action planning and in performing multistep activities of daily living. Consequently, prominent difficulties in action centrality, action sequencing and working memory may constitute the main treatment targets for improving the planning ability and actual performance of patients with anterior lesions in complex everyday action sequences. Our findings also support the predictions made by Grafman (1989; 1994) and Wood and Grafman (2003), that anterior lesions are related to insufficient production of RCA and deficient planning of complex script structures.

Our second goal was to explore the relation between several executive processes and the EDT script generation variables. Due to limitations in our sample size and the number of items included in each variable, the composition of our variables was based on findings from previous lesion and factor analytic studies with larger sample sizes and more items per factor (Wilson et al., 1996; Miyake et al., 2000; Stuss et al., 2001; Stuss and Levine, 2002; Bennett et al., 2005; Espinosa et al., 2009; Oosterman et al., 2012; 2013; Lezak, 1995; Bertens et al., 2015; also see the review of Alvarez and Emory, 2006 for standard executive measures).

Significant correlations were found between all the executive domains (‘Planning’, ‘Working Memory’, ‘Response generation’, ‘Inhibition’ and ‘Planning’) and RCA, PE and SE, indicating that RCA, PE and SE tap several executive functions. Furthermore, correlations between the five executive domains and RTA were not significant, suggesting that the inclusion of peripheral actions in an action-sequence does not depend on general executive functioning, in contrast with RI, which was significantly correlated with ‘Planning’, and ‘Productivity’. We also found that a higher ability to suppress IRI is significantly correlated with better performances on ‘inhibition’, ‘response generation’ and ‘planning’. This implies that the ability to withhold the
generation of intrusions irrelevant to a script scenario is not only dependent on inhibition but also presupposes adequate planning and response generation.

Additional multiple regression analyses, with EDT variables as dependent variables and executive domains as predictors, showed that RCA was significantly predicted by ‘Planning’, ‘Response generation’ and ‘Working Memory’. RI was significantly predicted by ‘Response generation’. PE was significantly predicted by ‘Response generation’ and ‘Shifting’. Finally, SE was significantly predicted by ‘Response generation’ and ‘Shifting’. RTA was not predicted by any executive domain. Taken together, these findings indicate, as expected, that verbal script generation taps several executive processes. However, the relative contribution of each of these processes to script generation varies for every EDT generation variable, supporting the multiple, but interrelated, components view of Executive Function in adults (Miyake et al., 2000).

These results suggest that the generation of relevant central actions in correct sequence without sequencing and perseverative errors demands various executive abilities such as the capacity to retrieve central actions in correct order (‘planning’), hold these actions on-line (working memory) while producing them in correct sequence (action plan), ‘shift’ (shifting/switching) from one essential action to the next in sequence and ‘inhibit’ (inhibition) intrusions from ‘breaking in’ throughout the on-going verbal script generation (Cooper and Shallice, 2000; Allain et al., 2011). More specifically, our data with respect to the crucial role of working memory in preventing intrusions, provide evidence for the predictions made previously by Zalla et al. (1998), Godbout and Doyon (2000), Godbout et al. (2004). These authors proposed that the generation of RI and IRI reflects a difficulty in ‘on-line’ comparison of action sequences retrieved from semantic memory with those to be actively maintained in working memory and produced in the actual task.

Our findings with respect to the contribution of shifting and response generation (consisting of semantic and phonemic fluency measures also dependent on set shifting) to the prevention of SE might also indicate that sequencing errors in verbal script generation tasks can be attributed to deficiencies in the semantic representation of action steps, as already suggested by Cosentino et al. (2006). Given the high verbal nature of the EDT, language expression (verbal fluency) should have been controlled for when examining group differences in script generation performance. This omission is a limitation of our study (and of other script generation studies) and an issue that should be addressed in future studies.

Finally, from a more practical perspective, our results reveal deficits in different aspects of EDT scripts after anterior brain damage. This can provide clinicians with useful qualitative information about the set of executive functions that is impaired when planning multistep real-life activities and thus needs to be assessed and treated when an improvement of goal-directed behaviour of patients with frontal lobe damage.
(e.g. TBI) in these situations is striven for.

In conclusion, verbal script generation tasks may be a useful tool for the assessment and treatment of executive dysfunctions visible in the planning of complex real-life tasks after anterior brain damage. However, this study has the limitation of examining only script generation without additionally comparing this to script execution. Consequently, future research should investigate both script generation and task execution in parallel, to explain difficulties in planning, execution and monitoring after brain damage in a more comprehensive way.
References


5

Updating of working memory in Goal Management Training: a new treatment for disorganized behaviour after brain damage
Abstract

**Background:** Disorganised behaviour and executive deficits hamper the independent cognitive functioning in multistep everyday activities. Goal Management Training aims to facilitate independent functioning in planning and executing complex everyday tasks.

**Objective:** (1) To apply the current approach of Goal Management Training to help brain-injured dysexecutive patients deal with problems in planning and thereby accomplish everyday multistep activities. (2) To introduce an updating memory technique in stage 4 of Goal Management Training, to facilitate the learning of stepwise action sequences in multistep daily tasks.

**Current treatment:** Dysexecutive patients are taught with the use of verbal and written instructions to apply Goal Management Training in five stages to improve their goal-directed behaviour.

**New treatment:** The combined treatment of Goal Management training with working memory strategies includes approximately 11 30-minute training sessions. Patients with executive problems are taught to apply an updating memory technique (image of a ‘ladder’) in the current training combined to accomplish two real-life multistep tasks. Patients are trained to use the memory technique, keep in working memory a sequence of steps previously acquired and integrate these with other steps uploaded in memory. Examples, instructions and guidance are provided about how this treatment should be administered.

**Discussion:** The usefulness of this new treatment in complex daily activities is discussed. Difficulties that may arise when administering this treatment and its generalization to new, non-trained daily situations are also considered. The efficacy of this treatment is currently being evaluated in a randomized control trial.
Introduction

Multistep activities of daily living demand higher-level executive abilities such as planning, maintaining and monitoring multiple steps (sub goals) in a sequence of actions leading to the final goal (goal-directed behaviour) (Levine et al., 2000; Sohlberg and Turkstra, 2011). Examples of multistep activities of daily living include the use of electronic devices or the preparation of a meal. Disorganized behaviour and deficits in goal management are often standing out as the most prominent executive problems in the daily life of patients with acquired brain injuries (Boelen et al., 2011; Levine et al., 2011). These deficits hamper multistep real-life tasks, in which behaviour is haphazard and not controlled by goals and subgoals constructed in response to environmental or internal demands (Robertson, 1996; Levine et al., 2000; 2011). The high prevalence of executive dysfunction in brain-damaged patients (Robertson, 1996; Levine et al., 1998; 2011; Bertens et al., 2013) and the considerable negative impact of such difficulties on multistep tasks (Robertson et al., 1996; Sohlberg and Mateer, 2011) have led to the development and application of a systematic intervention referred to as Goal Management Training (Duncan et al., 1986; Robertson, 1996). The efficacy of Goal Management Training in the treatment of everyday executive problems after acquired brain injury has been shown in several studies (Levine et al., 2000; 2007; 2011; va Hooren et al., 2007; Grant et al., 2012; Bertens et al., 2015). Within Goal Management Training, effective working memory performance is required for both the retaining and the ‘online’ checking of the sub goals leading to the successful attainment of end goals in multistep everyday tasks. Unfortunately, working memory deficits are often among the executive problems of many brain-injured patients, further impeding consistent behaviour towards the end goal of a task.

Here, we introduce an updating working memory strategy component in Goal Management Training with the aim to enhance the acquisition and effective application of Goal Management Training in the treatment of dysexecutive behaviour. This updating strategy is targeted at facilitating the learning and the maintenance of the steps necessary to complete multiple tasks in daily life.

Current Goal Management Training

Goal Management Training is a structured, interactive, and manual-based rehabilitation technique, based on Duncan’s theory (1986) of disorganization of behaviour following frontal lobe lesions (Robertson et al., 1996; Levine et al., 1998). Goal Management Training consists of 5 stages, with each stage corresponding to an important aspect of goal-directed behaviour, with the goal to structure the disorganized behaviour of patients with executive problems. This is achieved by systematically devising, ordering, carrying out and controlling the multiple steps of complex real-life tasks,
until the correct completion of these tasks (Robertson, 1996; Levine et al., 2011; Sohlberg and Matter, 2011; Bertens et al., 2013). A detailed description of these stages constituting Goal Management Training (along with the addition of the updating memory strategy in stage 4) is presented in Table 1.

The efficacy of Goal Management Training has been established in a series of seminal studies (Levine et al., 2000; 2011). Since then, Goal Management Training has been extensively used for the improvement of complex task performance after acquired brain injury in clinical rehabilitation (Levine et al., 2007; 2011; van Hooren et al., 2007; Fish et al., 2007; Robertson et al., 2007; Spikman et al., 2010; Boelen et al., 2011; Gratnt et al., 2012; Bertens et al., 2013; 2015). However, in order to successfully learn, maintain and carry out the steps of a complex task successfully, the final goal and the task sub goals (steps) have to be encoded and kept active in working memory, a short-term buffer that is usually affected in brain-injured patients with executive deficits (Sohlberg and Turkstra, 2011; Bertens et al., 2013).

A theory-driven approach to deficits in goal management: the incorporation of a working memory strategy in Goal Management Training

Working memory is a fundamental cognitive mechanism of temporary storage and maintenance of information, crucial in complex daily functioning (Dahlin et al., 2008; Netto et al., 2010; Klingberg et al., 2010). Its ‘updating’ component has been considered as one of the three major executive processes (Miyake et al., 2000).

Specifically, ‘updating’ goes beyond the simple maintenance of task-relevant information and consists in the requirement to actively manipulate this information in working memory rather than passively store it (Miyake et al., 2000). Updating is usually impaired in patients with executive deficits after acquired brain injury (Miller and Cohen, 2001), affecting the appropriate learning and activation of the steps (sub goals) which is needed in a particular stage of Goal Management Training (stage 4, see Table 1) (Dahlin et al., 2008; Netto et al., 2010; Klingberg et al., 2010; Sith, 2013). Therefore an updating training at this stage of Goal Management Training is expected to facilitate both the acquisition of new as well as the maintenance of previously uploaded information.

A new treatment: Goal Management Training with memory updating

Patients with acquired brain injury (traumatic brain injury, stroke, post-surgery tumours) in the chronic stage (over six months after onset) and persistent executive problems that were observed in daily living are eligible candidates for this new treatment. The patients are taught to apply the new treatment to two examples of real-life multistep tasks using the computer, as the majority of people nowadays have a previous background and are familiar with electronic devices.
Table 1  Goal Management Training stages.

Training in using the following scheme with ‘instructions’ in each stage:

1) ‘Orienting’ (self-awareness)  ‘STOP! What am I doing?’
2) ‘Defining the main goal!’  ‘Buying theatre tickets using the internet’
3) ’List the steps’  ‘Subdivide the main goal into sub goals and make a list’

1) Press the button to **turn the computer on**; STOP; CHECK;
2) **Connect with the internet and press** F2 (wireless connection) - **confirm** that you have access to the internet checking at the bottom on the right side of the screen; STOP; CHECK;
3) **Click on the** ; STOP; CHECK;
4) **Type in the** ‘www.google.com’ (the most used web browser) at the address bar’; STOP; CHECK;
5) **Enter key – word (s)** (e.g. the **title** of the wanted theatre play and ‘buy tickets’) into the Google search engine space; STOP; CHECK;
6) **Press** ‘enter/search’; STOP; CHECK;
7) **Select and click the first site in front of you**. e.g. the ‘www.elculture.gr’; STOP; CHECK;
8) **Select the target play** and click the ‘buying tickets on-line link (e.g. ’www.viva.gr’); STOP; CHECK;
9) **Select date/time**; STOP; CHECK; Continue;
10) **Select seats** (number, price); STOP; CHECK; Continue;
11) **Add to the basket**; STOP; CHECK;
12) **Press ‘Complete order’**; STOP; CHECK;
13) **Type in ‘Personal Information’** (name, surname, address, telephone number etc.). Continue;
14) **Select the type of your credit card**; STOP; CHECK;
15) **Enter your card’s number**; STOP; CHECK;
16) **Enter its expire date**; STOP; CHECK;
17) **Type in the CCV2 number** (3 last numbers of your card); STOP; CHECK;
18) **Select ‘Pay’**; STOP; CHECK;
19) **Confirm**.
The tasks are essential to be clearly subdivided into separate, sequential and achievable sub goals (steps). The first real-life multistep activity, task 1A, consists of 19 consecutive steps and is about ‘processing and buying theatre tickets using a website in the internet’, whereas the second one, Task2A, is a 15-step task entailing the ‘processing and sending an e-mail message to a friend’. A score of less than 6 sequential correct steps in each of these tasks is considered as an evidence of disorganised behaviour and a criterion to-be-involved in this treatment.

Goal Management Training with memory updating into practice
The new treatment of Goal Management Training with the incorporation of working memory strategies consists of 11 sessions. Patients are seen individually for thirty-minute sessions, at least three to four times a week. All sessions take place at the outpatient departments of the participating centres.

Content and characteristics of the new training
Training session 1: Goal Management Training algorithm in training task 1A
To begin with, based on the Goal Management Training clinical manual (Robertson, 1996), the trainer presents the Goal Management Training algorithm and its stages orally and in written form (please see Table 1) giving concrete examples of everyday activities that consist of multiple steps and explain that it is difficult to organize and
keep in mind (working memory) all these steps in the correct order without using this abstract schema (‘mental blackboard’). One of the possible examples the trainer can use to help the patients better understand the notion of their difficulties in everyday life and the usefulness of this treatment is the following:

‘Most people from time to time may face difficulties in keeping in mind what it is they are supposed to be doing. One example is trying to follow instructions for installing an electronic device you have bought. Another of several examples is trying to follow instructions for using the internet in a variety of on-line activities and transactions, such as ‘buying something, for instance theatre tickets, from a website’ (see training task 1A in table 1). The following instructions (see the 19 steps of training task 1A in table 1) can be an arduous problem for anyone who has tried to memorize them and do what it is needed according to these instructions’.

After the presentation of the Goal Management Training scheme, using concrete examples of its application, the trainer coaches the patients to systematically follow the instructions given in each stage of Goal Management (see table 1). This is achieved by teaching trainees to use simple catchphrases that they are asked to come up with, such as ‘Watch it’, ‘Look out’, ‘Stop, what am I doing?’ ‘Think!’, ‘List the steps’, ‘Learn he Steps; Stop; Check’ (Robertson et al., 1996). The trainer first presents the instructions provided in each stage verbally and in written cards. Then the patients are asked to verbally repeat the instructions of each stage and later to repeat them with inner voice as ‘internal’ self-guidance. For instance, in stages 1 and 2 the trainer prompts the patients to think of what they intend to do (training task 1A), repeat this main task and keep it clearly in their memory. Later, in stage 3 they are asked to subdivide and list the multiple sub goals (steps) of task 1A in a correct sequence (see table 1).

After this stage, that is when the trainer tries to introduce stage 4 (learning phase), some patients may find it difficult to learn and retain the written list of all the steps in a sequence, the sheer number of steps exceeding their memory load (Sohlberg and Turkstra, 2011). However, it is necessary the patients to be informed that: (a) the large amount of information is going to be segmented in order to facilitate the retention of the steps and (b) a specific strategy is going to be applied for this purpose.

**Training session 2: Introduction and practice of a working memory updating strategy: the steps of a ladder metaphor**

During this session (see tables 1 and 2) the examiner introduces the updating working memory strategy, integrated in stage 4 of the Goal Management Training scheme. This strategy entails the presentation of the visual image of a ladder with four steps and key-words written on each step (representing the first four sub goals of task 1A). The following instructions are provided in verbal and written form, explaining this strategy and its usefulness in stage 4 of Goal Management Training:
‘Now we are going to learn the steps of the complex task presented in the previous session. To help you memorize the steps of this task, we are going to use this ladder (see Table 1). It will help you to learn and keep the steps in mind. Each step of the ladder represents a sub goal toward your main goal. A key word for each sub goal is written on each step of this ladder. You are going to learn and retain the first four key-words on each step in a sequence until you know them by heart and can carry out these first four steps of the task. Try to remember, check and move from one step to another. When you achieve this, you are going to learn the next steps, also in sequence.’ Then, the examiner has to pronounce the key – words aloud (see table 1) and ask the patient to verbally repeat them, one by one. The examiner should also encourage the patients to learn and use the following instructions provided in verbal and written form:

1. LOOK at the first step, examiner verbalizes key-word;
2. Say aloud, repeat, and keep!;
3. STOP. Ok? Move on!;
4. Second step – second key-word, verbalized by examiner. Say aloud, repeat, keep;
5. Combine! Repeat and keep the combination;
6. STOP. Ok? Move on!

Instructions like ‘Keep’, ‘Stop’ ‘Combine’ are additionally given in written cue cards. After the visual presentation and verbalization of the first four steps of the ladder (corresponding to the first four sub goals of task 1A), the trainer is going to describe and carry out (model) these steps in the correct order. Then the patients are required to verbalize and mimic what they should do on each of these steps, without actually performing the step. The described ladder-strategy, with written key-words on each step as well as the verbal and written instructions and modelling of the steps are provided by the trainer in a (feed-forward) errorless learning way, to prevent trial-and-error learning at this stage. Several studies have supported the efficacy of errorless learning compared to trial-and-error learning in patients with executive impairments after acquired brain damage of different aetiologies (Wilson et al., 1994; Kessels and De Haan, 2003; Dechamps et al., 2011; De Werd et al., 2013; Bertens et al., 2013; 2015).

Only then, the patients are asked to actually perform the steps and learn to check after each step if this has been correctly executed. Feed-forward verbal and written cues are also given by the trainer to prevent patients’ potential impulsive behaviours of moving to the next step without first checking the previous one. Only after the successful completion of a step, patients should move on to the next step until they effectively achieve all four steps. Thus, the patients are trained to use the technique of the ladder to learn (memorize) four steps and then carry them out in correct sequence.
Probe Session
Before training session 3, a probe session takes place in which patients are requested to recall the first four steps of the ladder previously acquired in session 2. These probe sessions are conducted before each training session, to ensure that patients can correctly carry out learned steps and are ready to learn the next steps. Errorless learning is directly applied every time the patient is doubtful or hesitates to perform a step. The examiner should not move on to the next sequence of steps (next training session) unless the successful accomplishment of the steps learned in the previous session (Sohlberg and turkstra, 2011).

Training sessions 3-11
The next four steps of task1A (fixed number of steps to-be-learned in each training session) are then uploaded in working memory and taught in the same way in every following training session (sessions 3-6), mainly focusing on the connection of the last step of the previous session with the four new ones in the sequence. This connection is illustrated in the image of the ladder using an arrow between the last learned and the new steps uploaded each time (please see figure 1). Patients are also given the following instructions: ‘Look at the ladder again and focus on the first

Figure 1 Uploading the next four steps (steps 5-8) of task 1A in training session 3 combined with the last step of the previous session (step 4) using an arrow.
step. This is the last step that you learned in our latest session. Now four new steps are added and you need to combine them with this step. The arrow helps you to remember the junction. It is important to keep this in mind.

The patients are instructed to repeat and retain this combination in working memory, until the successful completion of the whole task. Thus, they have to memorize and execute 5 four-step sets (5 training sessions using 5 images of a four-step ladder) in correct sequence instead of 19 separate steps, until the complete execution of the whole task. Consequently, the technique of the ladder is aimed at regularly updating (modifying) the content of working memory storage and it is used for simplifying and, thus, reducing working memory load in each training session.

An identical training approach (sessions 7-11) is applied for the acquisition of the second treatment goal, the 15-step task 2A.

The content of all training sessions is summarized in Table 2.

Discussion

Here, we incorporate an updating working memory strategy in one of the crucial stages of Goal Management Training (stage 4: encoding and learning the list of steps) with the aim to improve multistep task achievement. The effects of such an addition to Goal Management Training have not been examined so far.

This new combined treatment might be meaningful for patients with haphazard and disorganized behaviour, as a result of working memory deficits. These patients may benefit from a tailored training procedure, helping them to better organize and, thus, simplify a multistep task into smaller chunks of information (steps). The successive steps are anticipated to act as reminders of the former steps. Teaching an equal number of steps in each session is aimed at focusing the trainee on one set of steps at a time. This is expected to ensure the accurate acquisition of each set before moving to the next one.
Table 2 Structure and content of sessions designed for the new treatment.

<table>
<thead>
<tr>
<th>Experimental treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goal Management Training + Updating Working Memory strategy</td>
</tr>
<tr>
<td>1  Setting the treatment goals (task 1A and 2A)</td>
</tr>
<tr>
<td><em>Introducing the Goal Management scheme.</em></td>
</tr>
<tr>
<td>Defining stages 1, 2 and 3 (list of the 19 sub goals) of task 1A applying the Goal</td>
</tr>
<tr>
<td>Management scheme.</td>
</tr>
<tr>
<td>Subdividing task 1A into 19 steps (to-be-learned).</td>
</tr>
<tr>
<td>2  <em>Incorporating the updating working memory strategy</em> (image of a ladder) in stage 4</td>
</tr>
<tr>
<td>of GMT. Education in *learning the first four steps of task 1A as the first four</td>
</tr>
<tr>
<td>steps of the ladder.*</td>
</tr>
<tr>
<td>Systematic use of external faded gradually to internal mnemonic and errorless</td>
</tr>
<tr>
<td>learning techniques..</td>
</tr>
<tr>
<td>Adequate practice trials in actual performing the first four steps of task 1A.</td>
</tr>
<tr>
<td><em>Monitoring and Checking</em> after each step.</td>
</tr>
<tr>
<td>3  <em>Probe session:</em> Performing the steps learned in the previous session.</td>
</tr>
<tr>
<td>4-6 Similar therapeutic procedure until the successful learning and completion of all</td>
</tr>
<tr>
<td>steps of task 1A.</td>
</tr>
<tr>
<td>7  Applying stages 1, 2 and 3 of GMT to task 2A</td>
</tr>
</tbody>
</table>
In this way, patients are taught to adequately regulate processing load supporting executive control in working memory.

Executive impaired patients often face difficulties in initiation and commit perseverative errors. Some patients have problems in starting up a multistep activity, may get lost in a particular step or hesitate to move forward to a next step. Therapists should be aware of these problems and provide active guidance in such cases. For example, by emphasizing the use of arrows showing the connections between the four-step sets and learning techniques such as repeated visual (and verbal) cues (cards, oral instructions). Additionally, more attention should be given to the steps that are difficult to learn. Errorless learning and intensive, repeated practice are provided to make sure the patient successfully performs these steps.

One of the major problems that may arise during the training sessions is impulsivity. Patients may already move on to the next step or set of steps without monitoring and checking the outcome of their previous actions. Regaining self-control is important when improvement of disorganised behaviour is pursued. Thus, the therapist must pay attention to impulsive reactions, like giving the first answer that comes to mind or being easily distracted and confused. In this case it is helpful to introduce ‘STOP and Check’-moments after the completion of steps, before moving to a next step. The therapist may provide these instructions verbally or on written cards, even before impulsive reactions are seen. It is also important to stimulate patients to gradually use self-instruction to enhance self-awareness and on-task oriented behaviour. The number of steps ‘to-be-uploaded’ in each learning trial may also be modified, according to the needs and the severity of working memory impairment of each patient as well as the complexity of the task. Thus, the patients’ individual working memory capacity should be assessed as accurately as possible to adjust the set of information uploaded. Therapists must then appropriately teach their

Table 2  Continued.

<table>
<thead>
<tr>
<th></th>
<th>Learning and actual performing the first four steps of task2A applying the GMT with the addition of the updating training in stage 4, similarly to the treatment procedure of task 1A.</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>9-11</td>
<td>Same therapeutic procedure in all the following training sessions till the adequate learning and sequential execution of the 15 steps of task 2A.</td>
</tr>
</tbody>
</table>
patients to apply the combined treatment to minimize the amount of memory load to be learned in each session.

Eventually, therapists and specially trained proxies should prompt patients to use the treatment principles in real-life situations whenever a multistep everyday task has to be achieved. It is also their care to systematically check whether the patients effectively apply Goal Management Training with working memory strategies or use self-instructions in everyday tasks by observing and recording their patients’ executive behaviours as often as possible. Consequently, therapists and family members should persistently provide adequate practice and time, cues and feedback, whilst ‘on task’ behaviour takes shape.

The efficacy of this updating Goal Management Training is being currently evaluated in a randomized control trial.

**Clinical messages**

- Combining Goal Management Training with an updating working memory strategy may improve the handling of multistep activities of daily living after acquired brain damage.
- Therapists should be aware of their patients’ working memory deficits that may prevent the adequate acquisition and execution of multistep real-life tasks. The steps ‘to-be-learned’ should be presented and acquired in various, smaller sets of information in different ‘learning’ sessions.
- Therapists and proxies should be also appropriately trained in recognizing their patients’ difficulties and encourage them to generally use this combined treatment approach whenever they face difficulties to complete complex daily activities.
References


Incorporation of a working memory strategy in Goal Management Training to facilitate serial-order behaviour of brain-injured patients

CHAPTER 6

Abstract

Introduction: Goal Management Training (GMT) has been proven efficient in improving disorganized behaviour in multistep real-life tasks after brain damage. Here we incorporated Working Memory Training (WMT) in GMT to explore its combined efficacy in facilitating the serial-order maintenance of the steps-to-be-learned in GMT. The GMT+WMT was compared to a control WMT designed for other purposes.

Methods: 18 brain-injured patients (aged 20-54) in the chronic stage were randomly assigned to either the GMT+WMT or the WMT after a baseline score of less than 6 correct steps on each of two multistep everyday tasks 1 and 2 used as the primary outcome and training tasks in the GMT+WMT condition. Pre-treatment and post-treatment comparisons in each of these primary tasks and in several secondary and ‘additional’ neuropsychological measures were conducted.

Results: At post-treatment the GMT+WMT group performed significantly better than the WMT on the primary outcome measures and on ecologically-valid executive measures that demand a step-by-step maintenance of multiple actions. Time effects were found for both groups on the secondary measures. Non-significant differences were found for the rest of the measures.

Conclusions: Given the limitations, our results support the efficacy of the combined GMT+WMT in facilitating performance in everyday multistep tasks.

Key words: Goal Management Training, working memory training, daily executive dysfunction, disorganized behaviour, updating subgoals, multistep activities of daily living.
Introduction

Multistep activities of daily living demand intact executive functions, including planning, generation, inhibition, and monitoring of multiple steps (subgoals) in a sequence of actions leading to the final goal (Levine et al., 2000; Sohlberg and Turkstra, 2011). Examples of everyday multistep activities include the use of electronic devices or the preparation of a meal. Disorganized behaviour and deficits in goal management stand out as the most prominent executive problems in the daily life of patients with acquired brain injuries (Mateer et al., 1987), as a result of deficient action planning, impulsive and desultory behaviour (Levine et al., 2000). Thus, executive difficulties often obstruct the successful learning and execution of multistep real-life tasks (Sohlberg & Turkstra, 2011) and hamper the functional independence of brain-injured patients (Fasotti & Spikman, 2002; Spikman et al., 2010). The high prevalence of such deficits in brain-damaged patients (Levine et al., 2000; Bertens et al., 2013) underscores the need for developing effective interventions.

To improve goal-directed behaviour in complex real-life situations, Robertson (1996) developed Goal Management Training (GMT). GMT is a structured, interactive, manual-based intervention based on Duncan’s (1986) theory of disorganization of behaviour following frontal lobe lesions. The intervention is aimed at restructuring the disorganized behaviour of dysexecutive patients in complex real-life tasks (Levine et al., 2000). This aim is achieved by teaching patients to systematically devise, plan, and achieve the multiple steps of complex real-life tasks, until their correct completion. GMT consists of 5 stages (see Appendix A), with each stage corresponding to an important aspect of goal-directed behaviour. The efficacy of GMT in the treatment of everyday executive problems after acquired brain injury has been shown in several studies (Levine et al., 2000; 2007; 2011; Fish et al., 2007; van Hooren et al., 2007; Spikman et al. 2010; Grant et al., 2012, Bertens et al., 2015).

However, in addition to the regulation of behaviour, working memory plays a crucial role in the attainment and maintenance of the to-be-learned subgoals in GMT. Updating goals and subgoals in working memory is considered as one of the three major executive processes (Miyake et al., 2000), whereas impairments in working memory are frequently reported in patients with brain injury (Miller & Cohen, 2001; Sohlberg & Turkstra, 2011; Bertens et al., 2013). Thus, losing track of the steps in an on-going multistep everyday activity or having difficulties in staying focused on a sequence of subgoals/steps are examples of working memory problems that impede learning and executing subgoals in GMT (Dujardin et al., 2004, Dahlin et al., 2008; Netto et al., 2010; Smith, 2013; Tuedsson & Strohmayer, 2013). Hence, difficulties in goal-directed behaviour combined with working memory problems may together prevent the correct accomplishment of multistep everyday tasks.
However, combining GMT with a working memory strategy has not been attempted so far. In this study we introduce a working memory strategy training aimed at updating goals and subgoals in GMT. The aim of our study is to investigate the efficacy of this combined treatment, aimed at improving goal-persistent behaviour of brain-injured patients in complex everyday activities. The addition of an updating/working-memory strategy to GMT should facilitate the acquisition and maintenance of new to-be-learned steps along previously learned steps.

This combined treatment (referred to as GMT+WMT) will be compared with a regular working memory training (WMT) using everyday scenarios. The latter was not specifically designed to promote serial-order behaviour. Therefore, we expect GMT+WMT to be more effective than WMT in improving performance of multi-step everyday tasks in executively impaired brain-injured patients. The effects of both therapies on secondary executive and working memory outcome measures and several other neuropsychological tests of executive and cognitive function will also be investigated.

**Method**

**Design**
To investigate the efficacy of the combined treatment GMT+WMT, we performed a randomized controlled study in which we compared two treatments, that is, the GMT+WMT and WMT in everyday scenarios.

**Patients’ inclusion procedure**
Patients were recruited from several clinics in Thessaloniki, Greece. Patients with documented (on CT and/or MRI) acquired brain injury (ABI) (traumatic brain injury, stroke or post-tumour surgery) in the chronic stage (at least 4 months post-onset) were eligible to participate in this study. Patients with severe aphasia, neglect, severe psychiatric problems, neurodegenerative disorders and a history of substance abuse were excluded from this investigation (Spikman et al., 2010; Emmanouel et al., 2014). With respect to the post-surgery patients, subjects with sudden seizures and loss of consciousness prior to surgery were also excluded.

In addition to the ABI criterion, patients were further selected on the basis of their executive difficulties in everyday activities during sessions of physiotherapy and speech therapy, as observed by their therapists using a Greek-language version of Spikman’s Checklist of Executive Disorders (Spikman, 2002). This checklist is a structured interview completed by a therapist, in which questions are asked about several aspects of cognitive, awareness and psychosocial executive functioning in real-life. Based on this checklist, 23 brain-injured patients were initially recruited.
A third inclusion criterion was a baseline score of less than 6 sequential correct steps on each of two multistep everyday tasks used as the primary executive outcome measures in this study. These tasks were administered by the examiner using a computer. The first task was ‘to search and buy theatre tickets using a website in the internet’. It consisted of 19 steps (referred to as Task1, version A; Task1A). The second task (Task2, version A; Task2A) was ‘to send an email message to a friend’ and consisted of 15 steps. Five of the initial 23 patients did not meet the last-mentioned criterion (i.e., they achieved more than 6 correct steps in sequence) and were thus excluded from further participation. A flowchart of the study design is shown in Figure 1.

Eighteen patients (age ranging from 20 to 54 years, $M = 35$ years, $SD = 9$ years, men = 12, women = 6) entered treatment. Eleven had a traumatic brain injury (TBI), 1 a haemorrhagic stroke, 1 had undergone surgery for an aneurysm of the middle cerebral artery and 5 patients had a history of surgically resected focal brain tumours. All were in the chronic stage (post onset time ranged from 4 to 46 months, $M = 12.1$ months, $SD = 10.2$) and had sensorimotor and cognitive difficulties requiring treatment for at least 3 months. Eleven participants were outpatients of the Neurosurgical Department of Papanikolaou General Hospital, 3 were inpatients at the Rehabilitation Centre ‘Anagennisi’ and 4 patients were in treatment at the Rehabilitation Centre ‘Arogi’, all located in Thessaloniki, Greece. The TBI patients and the patient with a haemorrhagic stroke had suffered a period of loss of consciousness ranging from 12 to 33 days (coma duration, $M = 22.17$, $SD = 6.9$). The study was approved by the Scientific Directors of the participating centres and all participants provided written informed consent.

Randomization, blinding and outcome measures

The 18 patients were then randomly assigned to either the experimental treatment condition (GMT+WMT) ($N = 9$) or the control treatment condition (WMT) ($N = 9$).

Block randomization per groups of four (two ‘control’ and two ‘experimental’) took place by lot drawn blindly by a physiotherapist not involved in this study for the first sixteen patients and simple randomization (by tossing a coin) was applied for the last two patients. After performing the primary outcome tasks (Tasks 1A and 2A), participants also underwent an extensive pre-treatment assessment of executive and working memory abilities. This assessment included executive observational rating scales such as the Executive Observation Scale (EOS; Pollens, McBratnie, & Burton, 1988), the Role Resumption List (RRL; Spikman, Brand & Brower, 2002) and the Dysexecutive Questionnaire (DEX) self- and independent rater versions (Wilson et al., 1996), as well as working memory tests, that is, the Corsi Block Tapping Test (Corsi, 1972; Kessels et al, 2000), the WAIS-III Letter-Number Sequencing subtest (Wechsler, 1997), and a Greek version of a Letter 2-back (updating) task (see El Haj, Fasotti, & Allain, 2012). Moreover, several other executive, memory and language tests (Alvarez & Emory, 2006; Emmanouel et al., 2014) were administered (please see table 1).
To verify pre-treatment deficits in cognitive functioning, patients’ performances on the above-mentioned secondary outcome measures (except for the EOS and the RRL) were compared to those of a group of 12 healthy controls (HC) matched for age, years of education and IQ. No significant differences for demographic variables and IQ scores were found, as shown in table 2.

Figure 1 A flowchart of the treatment study.

* they did not meet the baseline inclusion criterion: they successfully executed more than the first 6 sequential steps on each of the primary baseline measures, i.e. Task 1A and Task 2A (used later as the main treatment goals in the experimental treatment condition).
**Procedure**

All tests and rating scales were administered in a fixed order before training (T0) by the neuropsychologist-examiner of this study.

Also prior to training, all patients were informed that two interventions were being compared, without further information. Rating scales were scored by the same physiotherapists who had completed Spikman’s Checklist and the DEX and who were blind to treatment allocation. The training sessions of the GMT+WMT and the WMT were given by the examiner-trainer of this study.

Tasks 1A and 2A were used as the main training tasks in the experimental treatment condition. Immediately after treatment (T1), alternative (B) versions of these multistep tasks were used as the main post-training (T1) outcome measures. Task1B was ‘to buy airplane tickets using the internet’ and Task2B was ‘to send a text message to a friend using a mobile phone’. The raw score on each of these tasks was rated on a two-point scale: (a) 1 point was given for every correct task step, that is every step successfully performed in correct sequence until the completion of the whole task and (b) 0 points for every incorrect step, that is a task step that was omitted, wrongly performed and/or executed in wrong sequence. Whenever a task step was incorrectly performed, visual feedback was provided by the website (the word ‘error’ written on the computer screen), without specific information about the nature of the error or how it could be fixed. Error notifications also prevented patients from moving on to the next step in sequence. They had to reflect about the error (was the step insufficiently performed or was it correctly executed but in the wrong order) and reformulate their response to the task step. No other feedback was given. If patients could not correct the error, their performance was recorded and scored by the examiner (i.e., the total number of correct steps executed in the correct sequence until that point) and the task was discontinued. If patients corrected the error and were able to continue, no points were given for the corrected step and the performance was scored as usual after that point.

The performances on post-training (T1) tasks1B and 2B were simultaneously recorded by both the examiner and an independent neuropsychologist who was blind for treatment allocation, basic principles, content and stages of both interventions. Additionally, all the tests, observation lists and questionnaires given by the examiner at pre-training (T0) were also administered immediately after training (T1) by the same independent neuropsychologist.

**Treatment Conditions**

Both treatments consisted of 11 sessions. Patients were individually seen in thirty-minute sessions, three to four times a week. All sessions took place at the outpatient departments of the participating centres and at patients’ homes. The content of the training sessions in both treatment conditions is summarized in Appendix B. A detailed
Table 1  Pre- and post-treatment outcome measures.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Screening</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Executive Checklist</strong> (Spikman et al., 2002)</td>
<td>total raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td><strong>Primary outcome measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(multistep everyday tasks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19-step Task1 performance</td>
<td>total number of correct steps in correct sequence (raw score)</td>
<td>x (A version)</td>
<td>x (B version)</td>
</tr>
<tr>
<td>15-step Task2 performance</td>
<td>total number of correct steps in correct sequence (raw score)</td>
<td>x (A version)</td>
<td>x (B version)</td>
</tr>
<tr>
<td><strong>Secondary outcome measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-Back task</td>
<td>raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Letter-Number Seq, WAIS-III</td>
<td>raw core + memory span</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Corsi Blocks Tapping Task</td>
<td>raw score + memory span</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Questionnaires</td>
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<tr>
<td>the Dysexecutive Questionnaire (DEX)</td>
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<tr>
<td>DEX-self</td>
<td>total raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>DEX-raters</td>
<td>total raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>EOS</td>
<td>total raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>RRL</td>
<td>total raw score</td>
<td>x</td>
<td>x</td>
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<tr>
<td><strong>Neuropsychological assessment</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Executive measures</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Trail Making Test B/A ratio</td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Digit B</td>
<td>raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Stroop Interference</td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>WCST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of Categories completed</td>
<td>raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>No. of Perseverative answers</td>
<td>raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Verbal Fluency Phon/Sem. ratio</td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>BADS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rule Shifting</td>
<td>raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Action Program</td>
<td>raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Key Search</td>
<td>raw score</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>
Table 1: Pre- and post-treatment outcome measures.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Recruitment</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoo Map Test</td>
<td>raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Modified Six Elements Test</td>
<td>raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Everyday Description Task</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Relevant Actions</td>
<td>raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>No. of Relevant Major Actions</td>
<td>raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>No. of Relevant Central Actions</td>
<td>raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>(major + minor)</td>
<td>raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>No. of Relevant Trivial (peripheral) Actions</td>
<td>raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>No. of Relevant Intrusions</td>
<td>raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Total Errors</td>
<td>raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>No. of Irrelevant Intrusions</td>
<td>raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>No. of Perseverative Errors</td>
<td>raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>No. of Sequencing Errors</td>
<td>raw score</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Memory and Language measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rey Auditory Verbal Learning Test (Learning 1-5, Short-Delayed Recall, Long-Delayed Recall, Recognition)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rey-Osterrieth Complex Figure Test (Immediate Recall, Delayed-Recall, Recognition)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit F</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vocabulary</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boston Naming Test-Short Form</td>
<td>x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: 19-step Task1: raw score of the total number of correct steps produced in Task1; 15-step Task2: raw score of the total number of correct steps produced in Task2; A & B versions: A = pre-treatment version, B = post-treatment version; 2-Back: Letter 2-Back Task; DEX-Self: the DEX completed by the participants themselves; DEX-raters: the DEX completed by an independent rater; EOS: Executive Observation scale total score; RRL: Role Resumption List total score; Trail Making Test B/A ratio: the Trail Making Test ratio of time to complete part B compared to the time to complete part A; Digit B: the Digit Span Backward, WAIS-III; Stroop Interference = StroopIII/II ratio of the total number of colours named in Condition III within the time limit of 45 seconds, compared to the colours named in Condition II within the same time limit (45 seconds) fixed for all the three Stroop Conditions according to Golden’s (1978); WCST: the Wisconsin Card Sorting Test; No. = Number of; BADS: the Behavioural Assessment of the Dysexecutive Syndrome battery (Wilson et al., 1996); Digit F: Digit Forward, WAIS-III; Vocabulary: Vocabulary subtest, WAIS-III; Boston Naming Test-Short Form in Greek (Tsapkini and Emmanouel, 2007).
description of the content, instructions and strategies used in the new treatment is available in the previous chapter. In short, for the GMT+WMT intervention, the GMT protocol was followed, adding a WMT strategy to stage 4 of GMT. On the other hand, for the WMT intervention, a new 9-step training was developed, aimed at improving patients’ performance on two real-life scenarios that engage working memory skills, that is Working Memory Task1 of ‘handling money in 19 sequential daily transactions’ (e.g. go for shopping, then pay bills etc) and Working Memory Task2 ‘distributing various boxes with supplies to 15 different cities of Greece’. These control WMT tasks consisted of the same number of steps as the experimental GMT+WMT tasks 1A and 2A.

### Statistical Analyses

Prior to analysis, all data (pre- and post-treatment) were tested for normality using Shapiro-Wilk’s normality tests. Skewed variables were thereupon transformed and again tested for normality. Negatively skewed variables were transformed using square transformation ($x^2$), whereas for positively skewed variables square root transformation was used (Clark-Carter, 1997). To explore pre-training (T0) group differences between the two treatment conditions on the primary outcome measures tasks1A and 2A and the secondary outcome rating scales EOS and RRL, all data (means and standard deviations) were analysed and compared using (1) independent-sample t-tests for normally distributed variables and (2) Mann-Whitney U tests (all one-tailed, $\alpha$ set at 0.05) for variables that remained skewed after transformation.

### Table 2: Mean Scores (+SD) and statistical comparison for demographic variables for the three groups at baseline.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HCs ($N=12$)</th>
<th>CTG ($N=9$)</th>
<th>ETG ($N=9$)</th>
<th>F (2, 27) &amp; p (1-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td></td>
</tr>
<tr>
<td>33.6 (9.16)</td>
<td>36.0 (10.1)</td>
<td>33.6 (7.9)</td>
<td>F = 0.224 p = 0.8</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>(years)</td>
<td>(years)</td>
<td>(years)</td>
<td></td>
</tr>
<tr>
<td>12.7 (2.1)</td>
<td>12.9 (1.4)</td>
<td>13.11 (2.2)</td>
<td>F= 0.13 p = 0.9</td>
<td></td>
</tr>
<tr>
<td>SPM-IQ</td>
<td>(years)</td>
<td>(years)</td>
<td>(years)</td>
<td></td>
</tr>
<tr>
<td>106.6 (6.6)</td>
<td>104.6 (6.3)</td>
<td>104.9 (6.7)</td>
<td>F = 1.5 p = 0.2</td>
<td></td>
</tr>
<tr>
<td>Sex m/f</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4/8)</td>
<td>(7/2)</td>
<td>(5/4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SPM-IQ: the estimated IQ scores of the Standard Raven’s Progressive Matrices; HCs: Healthy Controls; CTG: patients eligible for the control treatment group; ETG: patients eligible for the experimental treatment group; m/f: male/female ratio.
To investigate pre-treatment (T0) group differences among the three participant groups (HC, GMT+WMT and WMT) on neuropsychological test variables, secondary working memory outcome measures and the DEX, (1) parametric one-way ANOVAs and (2) non-parametric Kruskal-Wallis tests (all one-tailed, $\alpha = 0.05$) were computed. Post hoc comparisons were performed with Parametric Dunnet $t$-tests and non-parametric Mann-Whitney $U$ tests (all 2-tailed, $\alpha = 0.05$).

To examine the efficacy of the experimental treatment condition (GMT+WMT) and the control treatment (WMT in everyday scenarios), performance on the primary outcome measures tasks 1A and 2A (pre-treatment T0) and on post-training tasks 1B and 2B were analysed using a $2 \times 2$ General Linear Model (GLM) repeated measures analysis of variance. In this analysis ‘treatment condition’ (experimental and control) was used as between-subject factor and ‘time’ (pre-T0 and post-T1 training) as within-subject factor. Treatment effects were also examined by performing the same analysis separately for each of the secondary outcome measures and the other neuropsychological executive, memory and language variables. Appropriate post-hoc between-group and within-group comparisons (all two-tailed, $\alpha = 0.05$) were further conducted at post-treatment (T1), following significant GLM treatment $\times$ time interaction as well as main treatment and time effects. Effect sizes ($\eta^2_p$) were also reported according to Cohen’s (1988) criteria (0.1 = small effect, 0.3 = medium effect, 0.5 = large effect) (Cohen, 1992).

**Results**

**Pre-treatment analyses**

At baseline, the comparison between the performance of experimental and control group on the primary tasks 1A and 2A and the secondary outcome measures EOS and RRL did not result in any significant differences [all $t$-values (16) and $Z$-values $< 1.03$, all $p$-values $> .15$] (see table 3).

Pre-treatment post-hoc comparisons of the GMT+WMT and the WMT groups with the HC as well as between the two treatment groups on the other secondary outcome measures (that is the DEX-self, the DEX-other and the working memory tasks) and on the additional neuropsychological executive variables [after finding statistically significant group differences: all $F$-values (2,27) $> 4.8$, all $p$-values $< .016$; all $\chi^2$ (2) $> 17.9$, all $p$-values $< .0005$] revealed that while the HC outperformed both treatment groups on almost all these measures (all $p$-values $< .009$ in Dunnett t-tests; all $Z$-values $> -2.60$, all $p$-values $< .009$), no significant differences were found between the two treatment groups in all these measures prior to training (all $p$-values $> .37$) (see table 3 for the secondary outcome measures and table 4 for the other executive variables). The same pre-treatment analyses showed no statistically
Table 3  Results (means + SD) on the secondary EOS and RRL for the patients in the control treatment (WMT) and the patients in the experimental treatment (GMT+WMT). Results on the secondary outcome working memory measures and the DEX-Q for the healthy controls (HC), the WMT and the GMT+WMT groups. Post-treatment interaction and main effects (p-values) as well as significant pre- and post-treatment comparisons, $\alpha = .05$. 

<table>
<thead>
<tr>
<th>Pre-treatment</th>
<th>HC</th>
<th>WMT</th>
<th>GMT +WMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment (T0) Comparisons : WMT vs. GMT+WMT (2-independent samples, 1-tailed)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment (T0) pair-wise comparisons (2-tailed)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1: HC &gt; WMT*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2: HC &gt; GMT+WMT*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a: GMT+WMT &gt;WMT*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3b: WMT &gt;GMT+WMT*</td>
<td></td>
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</tr>
</tbody>
</table>

Secondary outcome measures

| Executive Observation Scale (total score) | 17.89 (3.06) | 17.44 (3.04) | n.s. |
| Role Resumption List | 15.22 (2.27) | 15.89 (2.14) | n.s. |
| Letter-Number Sequencing (WAIS-III) (raw score) | 13.17 (1.26) | 8.89 (1.90) | 9.22 (1.78) |
| Corsi Block Tapping Task (raw score) | 26.67 (4.14) | 18.22 (2.8) | 19.56 (1.94) |
| 2-Back task | 13.50 (0.67) | 11.22 (1.78) | 11.33 (1.22) |
| DEX Other | 5.33 (1.2) | 32.00 (8.10) | 33.67 (11.68) |
| DEX Self | 3.92 (1.08) | 9.56 (6.1) | 8.89 (2.4) |

Note: *: significant; ~: trend; n.s.: non-significant.

T0: pre-treatment

1 = Pre-treatment significantly better performances of HC vs. the WMT, results of T0 pair-wise comparisons (2-tailed), following significant T0 one-way ANOVAs and Kruskal-Wallis comparisons among HC, WMT and GMT+WMT.

2 = Pre-treatment significantly better performances of HC vs. the GMT+WMT, results of T0 pair-wise comparisons (2-tailed), following significant T0 one-way ANOVAs and Kruskal-Wallis comparisons among the three groups.

3a + 3b = Pre-treatment significantly better performances of the GMT+WMT vs. the WMT (and WMT vs.
### Table 3
Results (means + SD) on the secondary EOS and RRL for the patients in the control treatment (WMT) and the patients in the experimental treatment (GMT+WMT). Results on the secondary outcome working memory measures and the DEX-Q for the healthy controls (HC), the WMT and the GMT+WMT groups. Post-treatment interaction and main effects (p-values) as well as significant pre- and post-treatment comparisons, $\alpha = .05$.

<table>
<thead>
<tr>
<th>Pre-treatment (T0) pair-wise comparisons</th>
<th>Post-treatment (T1) Comparisons: Between groups:</th>
<th>Post-treatment (T1) Comparisons: Between groups:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment (T0) pair-wise comparisons</td>
<td>3a: GMT+WMT &gt; WMT*</td>
<td>3a: GMT+WMT &gt; WMT*</td>
</tr>
<tr>
<td></td>
<td>3b: WMT &gt; GMT+WMT *</td>
<td>3b: WMT &gt; GMT+WMT *</td>
</tr>
<tr>
<td>E: GMT+WMT &gt; WMT*</td>
<td>T0-T1 within-group differences:</td>
<td>T0-T1 within-group differences:</td>
</tr>
<tr>
<td>C: WMT T1 &gt; T0*</td>
<td>E: GMT+WMT T1 &gt; T0*</td>
<td>E: GMT+WMT T1 &gt; T0*</td>
</tr>
<tr>
<td></td>
<td>C: WMT T1 &gt; T0*</td>
<td>C: WMT T1 &gt; T0*</td>
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</table>

<table>
<thead>
<tr>
<th>WMT</th>
<th>GMT +WMT</th>
<th>Treatment × Time Interaction Effect (p-values)</th>
<th>Treatment Effect (p-values)</th>
<th>Time Effect (p-values)</th>
<th>Post-treatment (T1) Comparisons: Between groups:</th>
<th>Post-treatment (T1) Comparisons: Between groups:</th>
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<td>Treatment × Time Interaction Effect (p-values)</td>
<td>Treatment Effect (p-values)</td>
<td>Time Effect (p-values)</td>
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<td>3a, E, C</td>
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<tr>
<td></td>
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<td>.034*</td>
<td>.069~</td>
<td>.053~</td>
<td></td>
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</tr>
<tr>
<td>17.67 (2.00)</td>
<td>21.67 (2.95)</td>
<td>.855</td>
<td>.208</td>
<td>.009*</td>
<td>E, C</td>
<td>E, C</td>
</tr>
<tr>
<td>13.33 (1.5)</td>
<td>14.22 (0.83)</td>
<td>.294</td>
<td>.940</td>
<td>&lt;.0005*</td>
<td>E, C</td>
<td>E, C</td>
</tr>
<tr>
<td>10.78 (1.20)</td>
<td>10.56 (1.59)</td>
<td>.240</td>
<td>.368</td>
<td>&lt;.0005*</td>
<td>E, C</td>
<td>E, C</td>
</tr>
<tr>
<td>11.67 (1.22)</td>
<td>11.68 (1.32)</td>
<td>.818</td>
<td>.930</td>
<td>.121</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29.67 (8.29)</td>
<td>29.89 (10.56)</td>
<td>.075</td>
<td>.84</td>
<td>.0005*</td>
<td>E, C</td>
<td>E, C</td>
</tr>
<tr>
<td>9.33 (4.38)</td>
<td>7.78 (2.22)</td>
<td>.346</td>
<td>.564</td>
<td>.167</td>
<td></td>
<td></td>
</tr>
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</table>

GMT+WMT), results of T0 pair-wise comparisons (2-tailed), following significant T0 one-way ANOVAS and Kruskal-Wallis comparisons among the three groups.

**T1: post-treatment**

3a = Post-treatment significantly better performances of the GMT+WMT vs. the WMT, results of T1 post-hoc independent samples comparisons following significant GLM main and/or interaction effects.

E = Significantly better T1 vs. T0 performances within the GMT+WMT, results of post-hoc pair-samples comparisons following significant GLM main and/or interaction effects.

C = Significantly better T1 vs. T0 performances within the WMT, results of post-hoc pair-samples comparisons following significant GLM main and/or interaction effects.
Table 4 Results on the neuropsychological executive tests (means + SD) for the HC, the control WMT and the experimental GMT+WMT treatment groups, post-treatment interaction and main effects (p-values) as well as significant pre- and post-treatment comparisons, $\alpha = .05$.

<table>
<thead>
<tr>
<th>Executive Function Variables</th>
<th>HC</th>
<th>WMT</th>
<th>GMT +WMT</th>
<th>Pre-treatment (T0) Comparisons: WMT vs. GMT+WMT (2-independent samples, 1-tailed)</th>
<th>Pre-treatment (T0) pair-wise comparisons (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit B</td>
<td>8.00 (0.95)</td>
<td>6.00 (0.86)</td>
<td>5.44 (1.13)</td>
<td>1: HC &gt; WMT* 2: HC &gt; GMT+WMT* 3a: GMT+WMT &gt; WMT* 3b: WMT &gt; GMT+WMT*</td>
<td></td>
</tr>
<tr>
<td>Trail Making Test B/A ratio</td>
<td>2.12 (0.57)</td>
<td>2.82 (0.85)</td>
<td>3.18 (1.03)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Stroop Interference</td>
<td>0.59 (0.03)</td>
<td>0.422 (0.10)</td>
<td>0.423 (0.10)</td>
<td>1, 2</td>
<td></td>
</tr>
<tr>
<td>Wisconsin Card Sorting Test</td>
<td>No. of Categories completed</td>
<td>5.43 (0.06)</td>
<td>2.44 (0.72)</td>
<td>3.00 (1.32)</td>
<td>1, 2</td>
</tr>
<tr>
<td></td>
<td>No. of Perseverative Answers</td>
<td>12.42 (6.97)</td>
<td>70.44 (11.5)</td>
<td>59.56 (27.9)</td>
<td>1, 2</td>
</tr>
<tr>
<td>Verbal Fluency Phon./Sem. ratio</td>
<td>0.72 (0.09)</td>
<td>0.41 (0.08)</td>
<td>0.42 (0.08)</td>
<td>1, 2</td>
<td></td>
</tr>
<tr>
<td>BADS</td>
<td>Rule Shifting</td>
<td>0.65 (0.33)</td>
<td>2.78 (1.78)</td>
<td>3.00 (1.65)</td>
<td>1, 2</td>
</tr>
<tr>
<td></td>
<td>Action Program</td>
<td>4.75 (0.45)</td>
<td>2.78 (0.66)</td>
<td>3.33 (0.86)</td>
<td>1, 2</td>
</tr>
<tr>
<td></td>
<td>Key Search</td>
<td>14.58 (1.31)</td>
<td>11.44 (2.8)</td>
<td>10.89 (2.97)</td>
<td>1, 2</td>
</tr>
<tr>
<td></td>
<td>Zoo Map Test</td>
<td>15.08 (0.99)</td>
<td>10.67 (1.80)</td>
<td>10.00 (2.45)</td>
<td>1, 2</td>
</tr>
</tbody>
</table>

Note. *: significant; ~: trend.

T0: pre-treatment
1 = Pre-treatment significantly better performances of HC vs. the WMT, results of T0 multiple pair-wise comparisons (2-tailed), following significant T0 one-way ANOVAS and Kruskal-Wallis comparisons among HC, WMT and GMT+WMT.
2 = Pre-treatment significantly better performances of HC vs. the GMT+WMT, results of T0 multiple pair-wise comparisons (2-tailed), following significant T0 one-way ANOVAS and Kruskal-Wallis comparisons among the three groups.
3a + 3b = Pre-treatment significantly better performances of the GMT+WMT vs. the WMT (and WMT vs. GMT+WMT), results of T0 multiple pair-wise comparisons (2-tailed), following significant T0 one-way ANOVAS and Kruskal-Wallis comparisons among the three groups.
### Table 4

Results on the neuropsychological executive tests (means ± SD) for the HC, the control WMT and the experimental GMT+WMT treatment groups, post-treatment interaction and main effects (p-values) as well as significant pre- and post-treatment comparisons, \( \alpha = .05 \).

|                   | WMT       | GMT + WMT | Treatment × Time Interaction Effect (p-values) | Treatment Effect (p-values) | Time Effect (p-values) | Post-treatment (T1) Comparisons: Between groups:  
|-------------------|-----------|-----------|-----------------------------------------------|-----------------------------|------------------------|-------------------------------------------------------------------------------------------------------------------------------|
|                   |           |           |                                               |                             |                        | 3a: GMT + WMT > WMT*  
|                   |           |           |                                               |                             |                        | 3b: WMT > GMT + WMT*  
|                   |           |           |                                               |                             |                        | T0-T1 within-group differences:  
|                   |           |           |                                               |                             |                        | E: GMT + WMT T1 > T0*  
|                   |           |           |                                               |                             |                        | C: WMT T1 > T0*  
| Pre-treatment (T0) |           |           |                                               |                             |                        | 1: HC > WMT*  
|                   |           |           |                                               |                             |                        | 2: HC > GMT + WMT*  
|                   |           |           |                                               |                             |                        | 3a: GMT + WMT > WMT*  
|                   |           |           |                                               |                             |                        | 3b: WMT > GMT + WMT*  
|                   |           |           |                                               |                             |                        | Post-treatment (T1) Comparisons: Between groups:  
|                   |           |           |                                               |                             |                        | 3a: GMT + WMT > WMT*  
|                   |           |           |                                               |                             |                        | 3b: WMT > GMT + WMT*  
|                   |           |           |                                               |                             |                        | T0-T1 within-group differences:  
|                   |           |           |                                               |                             |                        | E: GMT + WMT T1 > T0*  
|                   |           |           |                                               |                             |                        | C: WMT T1 > T0*  

**Executive Function Variables**

| Test                          | WMT         | GMT + WMT | T0-T1 within-group differences: | T1: post-treatment | 3a – Post-treatment significantly better performances of the GMT + WMT vs. the WMT, results of T1 post-hoc independent samples comparisons following significant GLM main and/or interaction effects.  
|-------------------------------|-------------|-----------|--------------------------------|---------------------|-------------------------------------------------------------------------------------------------------------------------------|
| Digit B                       | 8.00 (0.95) | 6.00 (0.86) | 5.44 (1.13) | 1, 2                 | .756 (0.88) | .611 (0.99) | .548 (1.13) | .428 | .002* | .014* | 3b, C  
| Trail Making Test B/A ratio  | 2.12 (0.57) | 2.82 (0.85) | 3.18 (1.03) | 2                  | 2.72 (0.66) | 3.02 (0.99) | .548 | .428 | <.0005* | E, C  
| Stroop Interference           | 0.59 (0.03) | 0.422 (0.10) | 0.423 (0.10) | 1, 2                | 0.42 (0.09) | .4644 (0.075) | .351 | .476 | .351 |  
| Wisconsin Card Sorting Test   | 5.43 (0.06) | 2.44 (0.72) | 3.0 (1.32) | 1, 2                | 2.78 (0.66) | 3.56 (1.33) | .718 | .114 | .160 |  
| No. of Categories completed   | 12.42 (6.97) | 7.04 (11.5) | 5.95 (27.9) | 1, 2                | 1.89 (1.27) | 1.56 (1.33) | .620 | .906 | 0.050— |  
| No. of Perseverative Answers  | 4.75 (0.45) | 2.78 (0.66) | 3.33 (0.86) | 1, 2                | 3.00 (0.5) | 3.78 (0.83) | .677 | .09* | p = 0.222 | 3a  
| Verbal Fluency                | 0.72 (0.09) | 0.41 (0.08) | 0.42 (0.08) | 1, 2                | 13.67 (2.5) | 13.33 (2.34) | .898 | .641 | .015* | E, C  
| BADS                          | 0.65 (0.33) | 2.78 (1.78) | 3.00 (1.65) | 1, 2                | 11.56 (1.8) | 11.89 (1.96) | .464 | .810 | .053— |  
| Rule Shifting                 | 4.75 (0.45) | 2.78 (0.66) | 3.33 (0.86) | 1, 2                | 3.00 (0.5) | 3.78 (0.83) | .677 | .09* | p = 0.222 | 3a  
| Action Program                | 14.58 (1.31) | 11.44 (2.8) | 10.89 (2.97) | 1, 2                | 1.89 (1.27) | 1.56 (1.33) | .620 | .906 | 0.050— |  
| Key Search                    | 15.08 (0.99) | 10.67 (1.80) | 10.00 (2.45) | 1, 2                | 1.89 (1.27) | 1.56 (1.33) | .620 | .906 | 0.050— |  
| Zoo Map Test                  | 15.08 (0.99) | 10.67 (1.80) | 10.00 (2.45) | 1, 2                | 1.89 (1.27) | 1.56 (1.33) | .620 | .906 | 0.050— |  

**T0-T1 within-group differences:**

- **E**: Significantly better T1 vs. T0 performances for the GMT + WMT, results of post-hoc pair-samples comparisons following significant GLM main and/or interaction effects.
- **C**: Significantly better T1 vs. T0 performances for the WMT, results of post-hoc pair-samples comparisons following significant GLM main and/or interaction effects.
Table 4  Continued.

<table>
<thead>
<tr>
<th></th>
<th>HC</th>
<th>WMT</th>
<th>GMT+WMT</th>
<th>Pre-treatment (T0)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Comparisons :</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>WMT vs. GMT+WMT</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2-independent samples,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-tailed)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>Pre-treatment (T0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>pair-wise comparisons (2-tailed)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1: HC &gt; WMT*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2: HC &gt; GMT+WMT*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3a: GMT+WMT &gt; WMT*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3b: WMT &gt; GMT+WMT*</td>
</tr>
</tbody>
</table>

|                      |         |        |         |                      |
|                      |         |        |         | Treatment × Time     |
|                      |         |        |         | Interaction          |
|                      |         |        |         | Effect               |
|                      |         |        |         | (p-values)           |
|                      |         |        |         |                      |

### Pre-treatment

<table>
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<tr>
<th></th>
<th>HC (0.67)</th>
<th>WMT (0.60)</th>
<th>GMT+WMT (1.23)</th>
<th></th>
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<tr>
<td>Modified Six Elements Test</td>
<td>5.50</td>
<td>3.11</td>
<td>3.44</td>
<td>+WMT</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Everyday Description Task

<table>
<thead>
<tr>
<th></th>
<th>HC (5.98)</th>
<th>WMT (4.7)</th>
<th>GMT+WMT (5.78)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Relevant Actions</td>
<td>60.25</td>
<td>39.22</td>
<td>39.78</td>
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</tr>
<tr>
<td></td>
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<td></td>
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</tr>
<tr>
<td>No. of Relevant Major Actions</td>
<td>51.33</td>
<td>27.67</td>
<td>27.89</td>
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</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>No. of Relevant Central Actions</td>
<td>58.33</td>
<td>35.78</td>
<td>36.89</td>
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<tr>
<td></td>
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</tr>
<tr>
<td>No. of Relevant Trivial Actions</td>
<td>1.50</td>
<td>1.89</td>
<td>1.67</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of Relevant Intrusions</td>
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<td>2.56</td>
<td>1.56</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Errors</td>
<td>1.33 (0.88)</td>
<td>10.44 (1.87)</td>
<td>9.44 (1.95)</td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>No. of Irrelevant Intrusions</td>
<td>0.01</td>
<td>0.22</td>
<td>0.5</td>
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</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No. of Perseverative Errors</td>
<td>0.45</td>
<td>2.89</td>
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</tr>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No. of Sequencing Errors</td>
<td>1.08</td>
<td>7.33</td>
<td>5.67</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note.** *: significant; ~: trend.

**T0: pre-treatment**

1 = Pre-treatment significantly better performances of HC vs. the WMT, results of T0 multiple pair-wise comparisons (2-tailed), following significant T0 one-way ANOVAS and Kruskal-Wallis comparisons among HC, WMT and GMT+WMT.

2 = Pre-treatment significantly better performances of HC vs. the GMT+WMT, results of T0 multiple pair-wise comparisons (2-tailed), following significant T0 one-way ANOVAS and Kruskal-Wallis comparisons among the three groups.

3a + 3b = Pre-treatment significantly better performances of the GMT+WMT vs. the WMT (and WMT vs. GMT+WMT), results of T0 multiple pair-wise comparisons (2-tailed), following significant T0 one-way ANOVAS and Kruskal-Wallis comparisons among the three groups.
### Table 4

Continued.

<table>
<thead>
<tr>
<th>Treatment x Time Interaction Effect (p-values)</th>
<th>Treatment Effect (p-values)</th>
<th>Time Effect (p-values)</th>
<th>Post-treatment (T1) Comparisons:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMT</td>
<td>GMT</td>
<td>GMT + WMT</td>
<td></td>
</tr>
<tr>
<td>3.33 (0.5)</td>
<td>4.33 (0.5)</td>
<td></td>
<td>.269</td>
</tr>
<tr>
<td>42.33 (4.47)</td>
<td>45.44 (6.91)</td>
<td></td>
<td>.507</td>
</tr>
<tr>
<td>29.89 (3.72)</td>
<td>37.33 (5.65)</td>
<td></td>
<td>.058–</td>
</tr>
<tr>
<td>38.22 (3.38)</td>
<td>43.11 (6.71)</td>
<td></td>
<td>.281</td>
</tr>
<tr>
<td>2.00 (1.93)</td>
<td>1.89 (0.78)</td>
<td></td>
<td>.896, .786, .696</td>
</tr>
<tr>
<td>2.11 (2.37)</td>
<td>0.44 (0.25)</td>
<td></td>
<td>.668</td>
</tr>
<tr>
<td>9.56 (2.45)</td>
<td>6.56 (2.07)</td>
<td></td>
<td>.236</td>
</tr>
<tr>
<td>0.22 (0.4)</td>
<td>0.56 (0.08)</td>
<td></td>
<td>.587</td>
</tr>
<tr>
<td>2.67 (2.29)</td>
<td>2.89 (1.69)</td>
<td></td>
<td>.702</td>
</tr>
<tr>
<td>6.67 (1.2)</td>
<td>3.00 (1.41)</td>
<td></td>
<td>.122</td>
</tr>
</tbody>
</table>

**Post-treatment**

| WMT | GMT + WMT |  |  |  |  |  |
| 3a: GMT + WMT > WMT* |
| 3b: WMT > GMT + WMT* |

**T0-T1 within-group differences:**

| E: GMT + WMT T1 > T0* |
| C: WMT T1 > T0* |

**T1: post-treatment**

3a = Post-treatment significantly better performances of the GMT + WMT vs. the WMT, results of T1 post-hoc independent samples comparisons following significant GLM main and/or interaction effects.

3b: Post-treatment significantly better performances of the WMT vs. the GMT + WMT, results of T1 post-hoc independent samples comparisons following significant GLM main and/or interaction effects.

**T0-T1 within-group differences:**

E = Significantly better T1 vs. T0 performances for the GMT + WMT, results of post-hoc pair-samples comparisons following significant GLM main and/or interaction effects.

C = Significantly better T1 vs. T0 performances for the WMT, results of post-hoc pair-samples comparisons following significant GLM main and/or interaction effects.
Table 5 Results on memory and language variables (means + SD) for the HC, the control WMT and the experimental GMT+WMT treatment groups, post-treatment interaction and main effects (p-values) as well as significant statistical comparisons, $\alpha = .05$

<table>
<thead>
<tr>
<th>Pre-treatment</th>
<th>Pre-treatment (T0) Comparisons: WMT vs. GMT+WMT (2-independent samples, 1-tailed)</th>
<th>Pre-treatment (T0) pair-wise comparisons (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HC</td>
<td>WMT</td>
</tr>
<tr>
<td>Memory and language measures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Span Forward</td>
<td>10.00 (1.87)</td>
<td>9.58 (0.90)</td>
</tr>
<tr>
<td>Rey Auditory Verbal Learning Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials 1-5 (Learning)</td>
<td>55.00 (5.80)</td>
<td>52.22 (3.34)</td>
</tr>
<tr>
<td>Short-delay recall</td>
<td>12.58 (0.90)</td>
<td>11.78 (1.093)</td>
</tr>
<tr>
<td>Long-delay recall</td>
<td>12.00 (1.128)</td>
<td>11.56 (1.13)</td>
</tr>
<tr>
<td>Delayed recognition</td>
<td>13.17 (1.11)</td>
<td>12.67 (1.41)</td>
</tr>
<tr>
<td>Rey-Osterrieth Complex Figure Test</td>
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</tr>
<tr>
<td>Immediate recall</td>
<td>21.25 (1.91)</td>
<td>20.11 (2.47)</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>20.17 (1.69)</td>
<td>18.44 (2.69)</td>
</tr>
<tr>
<td>Recognition</td>
<td>10.58 (1.08)</td>
<td>10.00 (1.19)</td>
</tr>
<tr>
<td>Boston Naming Test – Short Form</td>
<td>13.67 (0.77)</td>
<td>13.00 (0.70)</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>49.25 (4.69)</td>
<td>45.89 (5.98)</td>
</tr>
</tbody>
</table>

Note. *: significant; ~: trend
T0: pre-treatment
2 = Pre-treatment significantly better performances of HC vs. the GMT+WMT, results of T0 multiple pair-wise comparisons (2-tailed), following significant T0 one-way ANOVAs and Kruskal-Wallis comparisons among the three groups.
### Table 5

Results on memory and language variables (means + SD) for the HC, the control WMT and the experimental GMT+WMT treatment groups, post-treatment interaction and main effects (p-values) as well as significant statistical comparisons, $\alpha = .05$

|                  | WMT        | GMT+WMT    | Treatment $\times$ Time Interaction Effect (p-values) | Treatment Effect (p-values) | Time Effect (p-values) | Post-treatment (T1) Comparisons: Between groups:  
|                  |            |            |                                                    |                            |                          | 3a: GMT+WMT > WMT*  
|                  |            |            |                                                    |                            |                          | 3b: WMT > GMT+WMT*  
|                  |            |            |                                                    |                            |                          | T0-T1 within-group differences:  
|                  |            |            |                                                    |                            |                          | E: GMT+WMT T1 > T0*  
|                  |            |            |                                                    |                            |                          | C: WMT T1 > T0*  

|                  |            |            |                                                    |                            |                          |  
| Pre-treatment    |            |            |                                                    |                            |                          |  
| T0               | 10.33 (1.22) | 10.78 (1.30) | .784                            | .527                          | .114                      |  
|                  | 52.00 (2.23) | 52.44 (4.27) | .428                            | .550                          | .525                      |  
|                  | 11.89 (1.26) | 11.11 (0.78) | .750                            | .048                          | 999                       |  
|                  | 11.89 (1.16) | 11.22 (1.09) | .787                            | .095                          | 589                       |  
|                  | 13.22 (1.39) | 12.89 (1.69) | .552                            | .925                          | 552                       |  
|                  | 22.33 (2.00) | 19.11 (5.3) | .468                            | .127                          | .233                      |  
|                  | 19.78 (3.03) | 17.56 (4.33) | .607                            | .234                          | .544                      |  
|                  | 10.44 (1.01) | 10.56 (0.72) | .410                            | .299                          | .619                      |  
|                  | 12.56 (0.72) | 13.78 (1.30) | .282                            | .009*                         | .715                      | 3a  
|                  | 46.11 (4.6) | 44.11 (6.5) | .529                            | .719                          | .619                      |  

**T1: post-treatment**

3a = Post-treatment significantly better performances of the GMT+WMT vs. the WMT, results of T1 post-hoc independent samples comparisons following significant GLM main training effects.
significant group differences among the GMT+WMT, the WMT and the HC in almost
the other memory and language variables [all \(F\)-values (2, 27) < 2.732, all \(p\)-values > 0.112; all \(\chi^2\) (2) < 4.218, all \(p\)-values > .121] (see table 5).

**Post-treatment analyses**

(a) Primary outcome measures

Figure 2 illustrates the pre- and post-training results (mean scores) of the primary outcome tasks 1 and 2 for the control and the experimental treatment groups. The results show that, compared to the absence of differences between the GMT+WMT and the WMT in primary outcome tasks 1 and 2 (‘A’ version) before treatment, after treatment significant ‘treatment’ and ‘time’ effects as well as a significant ‘treatment by time’ interaction effect were found for both tasks1 [all \(F\)-values(1, 16) > 46.1, all \(p\)-values < .0005, effect sizes \(\eta^2_p = .742 - .951\)] and 2 (‘B’ version) [all \(F\)-values(1, 16) > 27.244, all \(p\)-values < .0005, effect sizes \(\eta^2_p = .630 - .874\)]. Post-hoc comparisons revealed that post-training the GMT+WMT group performed significantly better than the WMT on primary outcome tasks 1 \([t (16) = 14.308, p < .0005, \eta^2_p = 0.96]\) and 2 \((Z = -3.610, p = < .0005, r = 0.86)\). A main ‘time’ effect was found within the GMT+WMT for both primary tasks 1 \([t (8) = -12.623, p = < .0005, \eta^2_p = 0.97]\) and 2 \([t (8) = -9.5, p = < .0005, \eta^2_p = 0.85]\), indicating that the patients included in the experimental GMT+WMT group performed significantly better on both primary outcome measures after training compared to pre-training conditions. No significant differences were found between post and pre-training performances on the same tasks for the WMT group.

(b) Secondary outcome measures

Table 3 shows the mean scores (and SDs) of both the WMT and the GMT+WMT groups on the secondary outcome measures after training and the results of GLM repeated analyses of variance. Main treatment and time effects as well as ‘treatment by time’ interaction effects (\(p\)-values) and post-hoc between-groups (GMT+WMT vs. WMT) and within-group comparisons (post-treatment vs. pre-treatment within-group differences) are also presented in table 3 (following significant GLM main and interaction effects).

After training a trend toward ‘treatment’ \([F (1, 16) = 3.8, p = .069, \eta^2_p = 0.192]\) and ‘time’ \([F (1, 16) = 4.3, p = .053, \eta^2_p = 0.215]\) effects was found for the EOS. No significant main ‘treatment’ or ‘treatment by time’ interaction effects were found for the RRL and the other secondary questionnaires and test measures. A significant ‘time’ effect was found for the RRL \([F (1,16) = 8.84, p = .009, \eta^2_p = 0.356]\) with both treatment groups attaining significantly better post-training psychosocial adjustment and reintegration \([t\text{-values} (8) > 2.08, p\text{-values}< .05]\). Similarly to the findings for the
RRL, only a significant ‘time’ effect was present for the DEX questionnaire (raters’ version), the Letter-Number Sequencing (raw score and memory span) subtest of WAIS-III and the Corsi Block Tapping Test (raw score) [all F-values(1, 16) > 37.3, all p-values < .0005, effect sizes $\eta^2_p = .70 - .848$]. After training, both treatment groups showed significantly better executive ‘behaviours’ and working memory performance on these variables compared to baseline [all t-values(8) > -2.72, all p-values < .026, all Z-values > -2.58, all p-values < .01].

**(c) Neuropsychological executive, memory and language test measures**

The same post-treatment statistical analyses were also performed on the executive tests (see table 4). With respect to these tests, significant main ‘treatment’ effects were found for the Digit Backwards WAIS-III subtest, the Action Program and the Modified Six Elements subtests of the BADS as well as for the total number of relevant major actions, the total number of errors and mainly the total number of sequencing errors produced in the EDT [all F-values (1, 16) > 5.07, all p-values < .039, effect sizes $\eta^2_p = .356 - .681$]. Post-hoc comparisons showed that after training the GMT+WMT performed significantly better on all these measures than the WMT [all t-values (16) > -2.80, all p-values < .013, all Z-values > -2.34, all p-values < .019], except for the Digit Backwards. Main ‘time’ effects were found for the Digit Backwards, the Trail Making Test Part B/A ratio, the Verbal Fluency Phonemic/ Semantic ratio, the Key Search subtest of the BADS, the total number of relevant major and central (major and minor) actions as well as the total number of errors produced in the EDT [all F-values (1, 16) > 5.07, all p-values < .039, effect sizes $\eta^2_p = .356 - .681$].

**Figure 2** Pre- and post-training results (means) on the primary outcome Task1 and Task2 for the control WMT and the experimental GMT+WMT treatment groups
Both treatment groups showed significantly better performances on these measures after training [all $t$-values(8) > -4.385, all $p$-values < .005, all $Z$-values > -2.02, all $p$-values < 0.043] except for the Digit Backwards and the total number of sequencing errors in the EDT. For the Digit Backwards only the WMT performed better after training [$t$ (8) = -3.7, $p$ = .005]. On the contrary, for the total number of sequencing errors in the EDT, only the GMT+WMT produced post-treatment significantly less sequencing errors compared to baseline [$Z$ = -2.023, $p$ = .043]. However, no significant ‘treatment by time’ interaction effects were found [all $F$-values (1, 16) < 2.66, all $p$-values > .12]. A trend for interaction was only found for the total number of relevant major actions produced in the Everyday Description Task (EDT) [$F$ (1, 16) = 4.183, $p$ = 0.058].

Regarding the memory and language variables (see table 5), neither main nor interaction effects were found except for a main ‘treatment’ effect on the Boston Naming Test-Short Form [$F$ (1, 16) = 8.6, $p$ = .009, $\eta^2_p = 0.352$]. Further comparisons showed that on this test the GMT+WMT performed significantly better than the WMT at post-treatment ($Z$ = -2.03, $p$ = 0.042).

**Discussion**

While several studies have shown beneficial effects of combining GMT with Problem-Solving Training (Spikman et al., 2010) or incorporating errorless learning strategies in GMT (Bertens et al., 2015), the combination of GMT and a WMT approach has not been examined so far. This combination, however, is highly relevant to study, since working memory is pivotal for both the maintenance of attention (persistent to the goal) and ‘online’ serial tracking of the sub-goals leading to the successful attainment of multistep everyday tasks (Netto et al., 2010; Klingberg, 2010). Therefore, in the present study we investigated the efficacy of a new combined treatment in which an updating working memory strategy was added to stage 4 (learning phase) of GMT. This new treatment (GMT+WMT) was compared to a control treatment of working memory training (WMT) in everyday scenarios in a randomized controlled study.

We found that after training the patients of the GMT+WMT group performed significantly better on two primary outcome multistep tasks 1 and 2 (B version) compared to the patients of the WMT group and compared to their own pre-treatment performance on the same tasks (A version). The WMT group showed the same performance level throughout. These results extend the findings of previous studies showing positive effects of GMT-based treatments on everyday behaviour of patients with acquired brain injury (Levine, 2007; 2011; Evans et al., 2007; van Hooren et al., 2007; Spikman et al. 2010; Grant et al., 2012). That is, our results show an effect of the combined GMT+WMT training on facilitating serial-order- and persistent behaviour in
non-trained variants of already acquired real-life executive tasks that involve maintenance and management of multiple subgoals in correct sequence. WMT, on the contrary, did not significantly improve the performance on such tasks. Hence, a combined GMT+WMT seems to be more effective on ameliorating performance in sequential real-life tasks than WMT only.

With regard to the effects on the secondary outcome measures used in this study, the improvement of the GMT+WMT training was only marginally significant on the EOS. The GMT+WMT group showed a minor improvement of on-task behaviour in several specific domains of executive functioning. This result could be attributed to the small sample size, possibly resulting in low statistical power. On all other secondary outcome measures (behavioural executive scales and working memory tests) we only found time effects, showing that training at task level does not necessarily lead to improvements in overt executive behaviour. As a general conclusion, despite the limitations of our small-scale study, the above findings are consistent with our proof-of-principle goal to provide evidence that the combined treatment of GMT+WMT is more helpful than a single WMT in improving performance on everyday multistep executive tasks.

We found significant training and time effects in favour of the WMT group on the Digit Span Backwards, a standard working memory task that is frequently used as a near-transfer task in many working memory training studies (review of Bopp & Verhaeghen, 2005; Netto et al., 2010). However, no beneficial effects were found on the other digit and spatial span tasks used as secondary working memory outcome measures in this study. This inconsistent finding is in line with the mixed results of many previous studies with respect to the efficacy of WMT training programs in ameliorating working memory capacities (digit span backward) (see the review of Shipstead et al., 2012; Zinke et al., 2013; McAvinue et al., 2013 Vermeij et al. (2015).

With respect to the other neuropsychological executive test results, significant training gains were found for the GMT+WMT in comparison with the control WMT on the BADS Action Program, the BADS MSET subtests as well as on an increased generation of major actions and a reduced production of sequencing errors in the EDT. These results are inconsistent with those of previous studies (Jelicic et al., 2001; Spikman et al., 2010) that showed only test-retest effects on the BADS subtests. However, they are in agreement with other studies (Manly et al., 2002; Hewiit et al., 2006) that applied a modified version of GMT and revealed intervention effects on the Six Elements Test (and its adaptations), as well as on planning and production of relevant steps in the EDT by TBI patients. Thus, our findings suggest that the positive effects of the GMT+WMT therapy are more obvious in ecologically valid and open-ended executive tests that demand a step-by-step maintenance and execution of complex everyday activities. This, combined with the finding that none of the treatment conditions had training or time effects on other, more traditional executive
tests (e.g. the Stroop Colour-Word Test, the Wisconsin Card Sorting Test) and on the majority of standard memory and language measures, underscores the conclusions of Spikman et al. (2010) about the difficulty of assessing daily functioning using conventional neuropsychological tests that lack adaptation to naturalistic settings. Therefore, we can conclude that executive tests mimicking real-life tasks, such as the BADS and the EDT, seem to provide more accurate information about the efficacy and the outcome of training programs designed to facilitate executive functioning in daily life.

In summary, our results support the efficacy of a combined treatment (GMT+WMT) in facilitating the performance of patients with ABI in everyday multistep tasks. The training also improves performance in more ecological executive tests, but not observed executive behaviour. Even though our results were partially expected, they should be interpreted with caution due to several limitations of our study. A relatively small sample size and an absence of follow up assessments do not allow drawing strong conclusions and predictions about the maintenance of training effects. Thus, the present blind randomized control study should be considered as an exploratory “proof of principle” study rather than a full-blown rehabilitation study. Future studies should investigate this further with larger samples and with follow-up measurements. With larger samples, the efficacy of the GMT+WMT approach can also be investigated in comparison with other interventions, for instance with GMT only. The results of this study also suggest that the GMT+WMT effects are more evident on real-life executive tasks (Levine et al., 2007). Therefore, when implemented in clinical practice the assessment of the results should prevalently rely on ecologically valid measures that involve everyday executive functioning. Future studies are also needed to assess the generalizability of this new treatment and the transfer of the skills acquired to other multistage everyday tasks not specifically targeted in the training, like ‘cooking a meal using the kitchen’ (like in Levine’s et al. study, 2000), or ‘setting the car alarm on’. Finally, another future aim could be to integrate this treatment in a larger, more comprehensive treatment (like Spikman’s multifaceted training based on GMT and Problem Solving Training) with the aim to investigate the enhanced effects on such an extensive treatment.
Appendix A  Goal Management Training stages using an example of multistep everyday task.

Training in using the following scheme with ‘instructions’ in each stage:

1) ‘Orienting’ (self-awareness)  ‘STOP! What am I doing?’
   Example:
2) ‘Defining the main goal!’  ‘Buying theatre tickets using the internet’
3) ‘List the steps’  ‘Subdivide the main goal into sub goals and make a list’

1) Press the button to turn the computer on; STOP; CHECK;
2) Connect with the internet and press F2 (wireless connection) - confirm that you have access to the internet checking at the bottom on the right side of the screen; STOP; CHECK;
3) Click on the ; STOP; CHECK;
4) Type in the ‘www.google.com’ (the most used web browser) at the address bar’; STOP; CHECK;
5) Enter key – word (s) (e.g. the title of the wanted theatre play and ‘buy tickets’) into the Google search engine space; STOP; CHECK;
6) Press ‘enter/search’; STOP; CHECK;
7) Select and click the first site in front of you, e.g. the ‘www.elculture.gr’; STOP; CHECK;
8) Select the target play and click the ‘buying tickets on-line link’ (e.g. ‘www.viva.gr’); STOP; CHECK;
9) Select date/time; STOP; CHECK; Continue;
10) Select seats (number, price); STOP; CHECK; Continue;
11) Add to the basket; STOP; CHECK;
12) Press ‘Complete order’; STOP; CHECK;
13) Type in ‘Personal Information’ (name, surname, address, telephone number etc.). Continue;
14) Select the type of your credit card; STOP; CHECK;
15) Enter your card’s number; STOP; CHECK;
16) Enter its expire date; STOP; CHECK;
17) Type in the CCV2 number (3 last numbers of your card); STOP; CHECK;
18) Select ‘Pay’; STOP; CHECK;
19) Confirm.

4) ‘Learn the steps’  ‘Do I know the steps now? If yes, move on to stage 5; if not, return to stage 4 and try again’

5) ‘Monitoring and Checking’  ‘Do It and Check!’
   (‘Am I doing what I planned? Check if yes or no; if yes, ok; if not, return to stage 1 and try again’)

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### Appendix B  Content of all sessions for both treatment conditions.

**Description of the therapeutic sessions**

<table>
<thead>
<tr>
<th>Experimental treatment</th>
<th>Control treatment</th>
</tr>
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<tbody>
<tr>
<td><strong>Goal Management Training + Updating Working Memory strategy</strong></td>
<td><strong>Training in everyday scenarios</strong></td>
</tr>
<tr>
<td>1 Setting the treatment goals (Task1A and Task2A)</td>
<td>Presentation of two ‘real-life’ WM Tasks, similar to tasks 1A and 2A (Task1 with 19 steps and Task 2 with 15 steps) as examples of daily living that demand retaining information in working memory. Presentation of a 9-stage Working Memory Training scheme aiming at improving these difficulties.</td>
</tr>
<tr>
<td><em>Introducing the Goal Management scheme.</em> Defining stages 1, 2 and 3 (list of the 19 sub goals) of task 1A applying the Goal Management scheme. Subdividing task 1A into 19 steps (to-be-learned).</td>
<td></td>
</tr>
<tr>
<td>2 <strong>Incorporating the updating working memory strategy</strong> <em>(image of a ladder)</em> in stage 4 of GMT. Education in learning the first four steps of Task1A as the first four steps of the ladder. Systematic use of external faded gradually to internal mnemonic and errorless learning techniques. Adequate practice trials in actual performing the first four steps of Task1A. <em>Monitoring and Checking</em> after each step.</td>
<td>Teaching the instructions given in each stage of the Working memory scheme with the use of visual and verbal cues. Education and practice provided in using this scheme for retaining and mentally manipulating previous and currently uploaded information (numbers) in examples of simple arithmetic problems.</td>
</tr>
<tr>
<td><strong>Probe session:</strong> Performing the steps learned in the previous session.</td>
<td></td>
</tr>
<tr>
<td>3 <strong>Uploading the next four new steps</strong> of Task1A as the next steps of the ladder. Systematic training in using the updating technique to learn and combine the new steps with those previously learned using arrows. Adequate practice trials to perform the 8 steps of Task1A learned so far. Monitoring and Checking after each step.</td>
<td>Introducing the first four activities (daily transactions) of Task1 using the 9-stage WMT scheme. Education in actively keeping the previous result with the new information while counting. Verbal feedback after each counting and emphasis on retaining the result from the last transaction until the next one.</td>
</tr>
<tr>
<td><strong>Probe session:</strong> Performing all the steps learned so far (8).</td>
<td></td>
</tr>
<tr>
<td>4-6 Similar therapeutic procedure until the successful learning and completion of all steps of Task1A.</td>
<td>Applying the same training in retaining the new memory load (four new transactions uploaded in session 4-6 and the last 3 activities (session 7) of Task1.</td>
</tr>
<tr>
<td>7 Applying stages 1, 2 and 3 of GMT to Task2A</td>
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## Appendix B  Continued.

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<tr>
<td><strong>8</strong></td>
<td>Learning and actual performing the first four steps of Task2A applying the GMT with the addition of the updating training in stage 4, similarly to the treatment procedure of Task1A.</td>
</tr>
<tr>
<td><strong>9-11</strong></td>
<td>Same therapeutic procedure in all the following training session still the adequate learning and sequential execution of the 15 steps of Task2A.</td>
</tr>
<tr>
<td></td>
<td>Dividing the 15-step Task2 into three sessions of 4 steps (activities) and a fourth session of the last 3 steps. Introducing the first four activities of the Task2. Same training in applying the Working Memory 9-stage framework for Task 2 as For Task 1.</td>
</tr>
<tr>
<td></td>
<td>Same procedure in all the following sessions for the same load (every 4 new arithmetic information uploaded) in each session.</td>
</tr>
</tbody>
</table>
References


Effective instructional methods. New York: Guilford Press.


Spikman, J.M., Brand, B., & Brouwer, W.H. (2002). Rolhervattingenlijst [Role Resumption List]. Internal Publication University Medical Centre Groningen, the Netherlands.
Summary and General Discussion
Main findings, limitations and future directions

The consequences of executive impairments in action planning, initiation, maintenance of action sequence within working memory, execution and monitoring of complex goal-directed activities are mainly evident in the everyday life of patients with moderate to severe traumatic brain injury (Bennett et al., 2005; Sbordone, 2010). Thus, the need for more accurate assessment of such difficulties in real-life settings has been highlighted (Wilson et al., 1996; Burgess et al., 1998; Chaytor et al., 2006; Spikman et al., 2010). Traditional neuropsychological tests used for the evaluation of executive disorders after acquired brain damage have generally proven valid in the effort to relate executive dysfunction to frontal lobe lesions in controlled assessment settings. However, their efficacy to capture these difficulties in ill-structured, open-ended and free-response everyday activities has been challenged (Chaytor and Schmitter-Edgecombe, 2003; Bennett et al., 2005; Chaytor et al., 2006; Chan et al., 2008; Sbordone, 2010). This criticism has led to the development of more ecologically valid executive tests and behavioural rating scales such as the Behavioural Assessment of Executive Syndrome (BADS) and the Dysexecutive Questionnaire respectively (DEX) (Wilson et al., 1996; Burgess et al., 1998; Alderman et al., 2003; Bennett et al., 2005; Chaytor et al., 2006). The latter tests and questionnaires were designed within an assessment approach putting more emphasis on everyday functioning, regardless of the localization of the brain damage (Wilson et al., 1996; Burgess et al., 1998). However, only a few studies have attempted to investigate the relation between deficient performance on these ecologically valid executive tests and anterior pathology so far.

Some of these studies have established the validity of the BADS test battery in detecting brain damage. This, by comparing the performance of groups of mixed, unselected brain-injured patients to those of healthy participants, used as controls (Wilson et al., 1996; 1998; Evans et al., 1997; Burgess et al., 1998; Norris and Tate, 2000; Boelen et al., 2009). However, these studies did not include patients with more focal damage and therefore did not study the relation between low performance on the BADS and anterior damage. On the other hand, a limited number of group studies found that the BADS is sensitive to neurological and psychiatric diseases presenting with dysexecutive symptoms related to anterior damage (Evans et al., 1997; Burgess et al., 1998; 2000; 2006; Ihara and Berrios, 2000; Cavanagh et al., 2002; Chan and Manly, 2002; Chan et al. 2003; 2004; 2006; 2008). Still, the conclusions drawn from these studies were restricted, due to the heterogeneous neurological and psychiatric samples included and the lack of comparison groups with lesions elsewhere in the brain. Only Bennett et al. (2005) administered the BADS battery (and the DEX) along with other traditional executive measures to 64 TBI patients, 24 of whom had documented anterior lesions and 40 had either documented lesions elsewhere in the
brain or no evidence of localized damage. However, the authors incorporated both patients with anterior lesions and patients with non-anterior lesions into one heterogeneous group and investigated the sensitivity of the BADS and other variables to executive dysfunction regardless of etiology and lesion location.

On the other hand, executive difficulties in real-life have been shown in patients with moderate to severe frontal lobe pathology after TBI, (Chaytor et al., 2006; Sbordone, 2010). Therefore, ecologically valid tests should be further investigated in terms of their ability to assess everyday executive dysfunction related to anterior brain damage. This could contribute to a more comprehensive assessment (and, thus, treatment plan) of the specific executive deficits and needs of frontally damaged patients in real-world settings. Only Channon and Crawford (1999) attempted to examine the sensitivity and specificity of the BADS and other real-life executive tasks in relation to lesion location. However, the results showed no significant group differences, a limitation that could be explained by the small sample size of the patient groups involved in the study (16 patients with anterior and 9 patients with posterior lesions).

Within this framework, the first three lesion studies of the present thesis investigated in a more systematic way the relation between deficient performance on two tasks, the BADS (including the DEX) and another everyday executive task, i.e. script generation, and anterior brain pathology. Therefore and contrary to previous studies including mixed, unselected brain-injured patients or small sample sizes, a higher number of patients with circumscribed brain lesions was recruited. Thirty patients with mainly focal anterior lesions and 22 patients with mainly posterior lesions were examined (as described in chapters 2, 3 and 4 respectively). Twenty-nine matched healthy adults were also included as controls. All our patients were signaled by their therapists as having everyday executive problems (with the use of the Spikman’s Executive Checklist screening). Also, as part of the screening procedure, all our patients (matched for age, education and general intellectual abilities), were found to have executive deficits compared to healthy controls in seven traditional executive tests. These traditional executive tests were considered as useful screening tools in identifying frontal lobe executive dysfunction (Banich, 1997; Stuss and Levine, 2002; Bennett et al., 2005; Alvarez and Emory, 2006). Additionally, the patients with anterior lesions performed significantly worse than those with posterior lesions on all the aforementioned tests. However, a limitation of our study (and other relevant studies) was that the proportion of patients with TBI in the anterior group was higher as compared with those included in the posterior group. This issue should be taken into consideration in future studies.

With regard to our main research goal, that is, the exploration of the relation between performance on real-life executive tasks and anterior damage, in our first lesion study (described in chapter 2) we compared the performances of the patients
with anterior lesions to those of the patients with posterior lesions on all the BADS executive subtests (and to those of healthy controls). We initially investigated which BADS executive variables are more sensitive and specific to anterior damage and, afterwards, which of these sensitive and specific executive variables are the best predictors of anterior pathology.

Our results showed that the executive function BADS subtests Rule Shifting, Action Program, Key Search and Zoo Map (total score) are sensitive, but not specific to anterior damage; this means that patients with anterior lesions performed significantly worse than posteriorly damaged patients on these BADS subtests. However, significantly worse performances on the same variables were also found in posteriorly lesioned patients when compared to healthy controls. These findings suggest that deficient performance on the BADS subtests Rule Shifting, Action Program, Key Search and Zoo Map is strongly related to dominant (but not only) anterior damage.

Additionally, the BADS Modified Six Elements Test (MSET) and the Map Zoo Map Test (Condition 2), were shown to be more specific to anterior brain dysfunction; we found that performance on these two BADS executive variables is significantly more impaired in patients with anterior lesions compared to patients with posterior lesions, whereas no significant differences were found on the same measures between the group of patients with posterior lesions and the healthy controls. Thus, low scores on these two ecologically valid executive variables are indicative for anterior pathology.

Finally, among all these variables, the BADS MSET was found to be the best predictor of anterior brain dysfunction. Therefore, poor performance on this ill-structured and open-ended BADS task can be solely used as an indicator of real-life executive impairment related to anterior pathology.

Our results seem to provide quantitative and qualitative data on specific aspects of everyday executive dysfunction related to anterior pathology. More precisely, the significantly worse performance of the anterior group on the BADS Rule Shifting, Key Search, Action Program, Zoo Map and Modified Six Element subtests may indicate impairments in specific executive domains such as: (a) **cognitive flexibility and set shifting** (as assessed by the BADS Key Search subtest; Wilson et al., 1996; 1998), (b) **action planning** (as measured by the BADS Action Program, Zoo Map and Modified Six Element subtests; Wilson et al., 1996; Espinoza et al., 2009; Oosterman et al., 2012; 2013; Bertens et al., 2015) and (c) **intentionality and inhibition** (as detected by the BADS Modified Six Element Test; Burgess et al., 1998; Andres, 2003). These findings imply that deficits in these executive domains may be facets of executive dysfunction severely interfering with the correct execution of real-life executive tasks in subjects with anterior pathology.

Hence, in our first study we attempted to determine the relation between everyday executive dysfunction and anterior damage in a more specific way. This issue has not
been investigated systematically so far, because previous studies were based on the examination of everyday executive dysfunction independently of lesion location. However, the need to explore the relationship between everyday executive disorders and lesion localization comes mainly from evidence of great difficulties in performing ill-structured everyday tasks after anterior injury (Sbordone, 2010). We addressed this research question by incorporating a number of well-selected patients with focal anterior lesions and focal posterior lesions. Direct comparisons between these two patient groups allowed us to derive more specific indices of executive function that can be used for the accurate assessment and treatment of everyday executive problems faced by patients with anterior lesions, as is the case of patients with TBI.

As an extension of the first study, the research goal of our second lesion study (described in **chapter 3**) was to examine the validity of behavioural measures of everyday executive problems, such as the Dysexecutive Questionnaire (DEX; Wilson et al., 1996) to identify differences in the severity of the daily dysexecutive symptoms according to the location of the brain damage (anterior vs. posterior). For this purpose, the same patient groups (and healthy controls) were also compared with respect to their ability to give reliable and valid self-reports on the frequency and severity of their daily dysexecutive behaviours as measured by the DEX. The DEX was also completed by therapists. We found no significant differences between DEX self-reports of patients with anterior and posterior lesions. This is in contrast with the findings of our first study that showed worse performance of the patient group with anterior lesions in executive tests. Additionally, in our second study, no significant correlations were found between the DEX self-reports of the anteriorly damaged patients and their executive performance on BADS executive variables and two other real-life executive tasks, the Everyday Description Task (EDT) and the Twenty Question Test (TQT). These results point to poor insight and awareness of deficits in patients with anterior lesions.

On the other hand, the therapists of the anteriorly injured group reported significantly more frequent and severe daily dysexecutive symptoms in their patients compared to the therapist judgments of the posterior group. The DEX reports of the therapists were also significantly associated with their patients’ deficient performance on the six BADS subtests, the EDT and the TQT. The strongest association was found between the DEX reports of the therapists and the BADS Modified Six Elements Test. These findings indicate that therapists of the anterior patient group can provide reliable information about the frequency and severity of their patients’ daily executive symptoms in clinical settings. Additionally, the DEX reports of the therapists combined with the BADS Modified Six Elements Test may potentially provide a brief screening for patients with severe executive problems. The Modified Six Elements Test is an open-ended and ill-structured planning task demanding **intentionality, inhibition, working memory, set shifting and time management**. These executive cognitive processes are also required in many complex activities of daily living and, thus, both
assessment and rehabilitation of daily executive deficits should focus on these key executive components. These findings are also consistent with the conclusions of our previous study suggesting that deficits in the same executive abilities (i.e., intentionality, inhibition, action planning, cognitive flexibility and set shifting) hamper the execution of real-life executive tasks. Thus, our first and second studies provide useful empirical data for a more accurate assessment and treatment of everyday executive dysfunction present in patients with anterior pathology.

In chapter 4 the relation between a free-response everyday executive task, script generation, and anterior damage was studied. Script generation is based on higher executive abilities such as action (step) planning, initiation, and sequencing. Thus, difficulties in script tasks may reflect deficits in planning, initiation, sequencing, updating of the sequential actions (steps) in working memory, execution and monitoring of goal-directed behaviour towards the completion of multistep everyday activities (Boelen et al., 2011; Allain et al., 2011). The results derived from our two previous lesion studies suggest that deficits in the aforementioned executive functions significantly hamper everyday executive performance of patients with anterior injury.

Several studies investigating script generation in relation to lesion location have provided consistent results regarding the relation between deficits in script sequencing (total number of sequencing and perseverative errors) and frontal-lobe pathology (Zalla et al., 1998; Allain et al, 2001; Zanini et al., 2002; Fortin et al., 2003; Godbout et al., 2004; Zanini, 2008). However, mixed results have been found in the investigation of the relation between the total number of correct actions generated in everyday scripts and frontal pathology. Clarifying this controversial issue, that is, whether there is a relation between script action generation and anterior damage, was the main aim of our third study. Therefore, we included patients with either focal anterior lesions (30 patients) or focal posterior lesions (22 patients). We compared the performance of these groups (and healthy controls) on verbal script generation by using eight multistep script tasks, all derived from the Everyday Description Task (EDT; Dritschel et al., 1998). Scoring of the scripts, described in the chapter 4, was also based on a method previously proposed by Boelen et al. (2011).

Multiple comparisons showed that patients with anterior lesions generated significantly less relevant central (more distinctive) actions in all the eight scripts when compared with the group of patients with posterior lesions and the healthy control group. Relevant central actions were also found to be the only significant predictor of anterior dysfunction. So, a deficiency or a loss of ‘centrality’ in the core of actions needed for the accurate planning and generation of an everyday script is characteristic for primary anterior pathology. We also found that patients with anterior lesions made significantly more perseverative and sequencing errors within the EDT scripts. These findings indicate that the reduced production of relevant central actions and an increased number of sequencing and perseverative errors within everyday script
tasks are sensitive indicators of anterior brain damage. These indices can be used for the assessment and treatment of deficits in action planning, sequencing and performing multistep activities of daily living.

The relation between these three script indicators of anterior damage and five composite executive variables was also explored. These variables represented Working Memory, Response generation, Inhibition, Shifting and Planning. The results showed that the three script indicators sensitive for anterior damage call upon all these executive functions. This highlights the crucial role of these five core executive domains in efficient planning and performance of multistep everyday tasks demanding the involvement of anterior brain regions.

However, a major limitation of our study (and previous relevant studies such as Boelen et al., 2011) was that verbal script generation was studied without investigating the performances of patients on the actual execution of the scripts. Some studies have shown that patients with executive disorders had problems with script generation, which were even more pronounced when they had to execute the scripts (Chevignard et al., 2000; Fortin, Godbout, & Braun, 2003). Patients made significantly more planning as well as execution errors (e.g., omissions, errors of context neglect, environmental adherence, commentaries) than control participants. These deficits are seen in daily life situations, but not in traditional neuropsychological tests. Verbal generation (verbalization of mental planning) and execution (execution while retaining the correct sequence of actions in working memory, monitoring and self-regulation) are the two basic aspects of scripts that make this task a more ecologically valid alternative to the majority of executive tests. Thus, future studies should investigate both script generation and the actual execution of scripts in a more comprehensive way (Boelen et al., 2011). In addition, another limitation of this study (and of other script generation studies) is that given the high verbal nature of the EDT, language expression (verbal fluency) should have been controlled for when examining group differences in script generation performance. This is also an issue that should be addressed in future studies.

Finally, to address the limitation of the higher ratio of patients with TBI within the anterior group compared to those included in the posterior group, we conducted subgroup analyses within the anterior group by comparing the performance of the patients with TBI to those of the patients with other etiologies included within this group on all the EDT script variables. No significant differences were found between the two patient subgroups of the anterior group.

Despite these limitations, the findings from this thesis may provide clinicians with useful qualitative information about which set of executive functions is impaired in planning and performing multistep activities of daily living and, thus, should be assessed and used as potential treatment targets in order to improve complex goal-directed behaviour of patients with anterior lesions.
Within this framework, we designed a treatment protocol (described in detail in chapter 5) aiming at further facilitating (a) the learning and maintenance of stepwise action sequences within working memory, as well as (b) controlled serial-order behaviour in multistep real-life executive tasks. Impulsive (uncontrolled), disorganized behaviour and deficits in working memory are central executive dysfunctions impairing performance on everyday functioning. Our treatment was intended to help patients adopt a more controlled approach to real-life tasks especially when tasks demand stepwise processing (Evans, 2003; Sohlberg and Matter, 2001; Sohlberg and Turkstra, 2011). In this treatment we incorporated an updating working memory strategy (WMT) in Goal Management Training (GMT), a well-studied algorithm used to improve goal-directed behaviour in multistep activities of daily living (Levine et al., 2011; Bertens et al. 2013). Particularly, the goal was to teach brain-injured patients with executive problems to systematically use a visual imagery technique gradually faded to an internal mental representation (i.e., memorize the metaphor of a ladder) in stage 4 (learning of subgoals in correct sequence) of GMT. Training of this technique using errorless learning principles as well as full instructions and description of the treatment stages and sessions are presented in detail in chapter 5. This combined treatment of GMT + WMT was hypothesized to further help brain-injured patients to retain and monitor the correct sequence of subgoals needed for the completion of a multistep everyday task, as working memory is one of the core executive functions affected in acquired brain injury.

Thus, as described in chapter 6, we designed a randomized control study to investigate the effectiveness of this new combined treatment GMT + WMT (experimental treatment condition) compared to a control working memory training (WMT) with everyday scenarios designed for other purposes. Initially, twenty-three patients were recruited to participate in this study. All these patients had CT or MRI documented acquired brain damage of mixed etiology (traumatic brain injury, stroke or post-tumour surgery) in the chronic stage (at least four months post-onset) and were signalled by their therapists as having everyday executive difficulties (using a Greek-language version of Spikman’s Checklist of Executive Disorders). However, using the inclusion criterion of a baseline score of less than 6 correct steps on each of two multistep everyday tasks 1 and 2 (used both as the primary outcome and the training tasks in the experimental treatment condition), eighteen patients were finally selected to participate. These patients were then randomly assigned to either the experimental treatment condition (GMT+WMT) \((N = 9)\) or the control treatment condition (WMT) \((N = 9)\). Participants also underwent an extensive pre-and post-treatment assessment, including several executive behavioural scales and working memory tests as secondary outcome measures as well as additional executive, memory and language tests, all illustrated in chapter 6.
The results of our RCT show that after training the patients of the GMT+WMT group performed significantly better on new versions (version B) of the two primary outcome multistep tasks 1 and 2 compared to the patients of a control WMT group and compared to their own pre-treatment performance on the same tasks (A version). On the other hand, no improvement in the same tasks was observed in the control WMT group. These findings indicate an effect of the combined GMT+WMT training on facilitating serial-order- and persistent behaviour in non-trained variants of already acquired real-life executive tasks that involve maintenance and execution of multiple subgoals in correct sequence. Our results are in agreement with those of previous treatment studies showing positive effects of GMT-based or GMT-combined treatments on everyday behaviour of patients with acquired brain injury (Levine, 2007; 2011; Evans et al., 2007; van Hoooren et al., 2007; Spikman et al. 2010; Grant et al., 2012; Bertens et al., 2015). With respect to the secondary outcome measures, only the GMT+WMT group showed a minor improvement on several aspects of on-task executive behaviour as evaluated by an Executive Observation Scale. We only found time effects on all other secondary measures. However, this could be attributed to our small sample size that may have limited the statistical power of these results.

With respect to the other executive tests, the results of chapter 6 revealed a significant training effect of GMT+WMT in comparison with the control WMT on the BADS Action Program, the BADS MSET subtests as well as on an increased generation of major actions and a reduced production of sequencing errors in the Everyday Description Task. These findings are in agreement with other studies (Manly et al., 2002; Hewiit et al., 2006) that revealed positive intervention effects of a modified version of GMT on the Six Elements Test (and its adaptations), as well as on planning and production of relevant steps in the EDT by TBI patients. Finally, none of two interventions had either training or time effects on other, more traditional executive tests (such as the Stroop Colour-Word Test or the Wisconsin Card Sorting Test) and on the majority of standard memory and language measures. This underscores the conclusions of many previous researchers (Chaytor and Schmitter-Edgecombe, 2003; Chaytor et al., 2006; Sbordone, 2010; Spikman et al. 2010) about the failure of conventional neuropsychological tests to capture executive difficulties in daily functioning due to their lack of ecological validity.

In conclusion, our results, even though limited by our small sample size and our proof-of-principle goal showed that the new combined GMT+WMT treatment has clearly positive effects on more ecologically valid executive tasks that demand maintenance and execution of sequential steps towards the completion of everyday activities.

Our treatment study has several limitations and the results of our RCT should be discussed and interpreted within this perspective. First of all, our relatively small sample size and the lack of follow up assessments do not enable us to draw
comprehensive conclusions and predictions about the maintenance of training effects. Thus, the present treatment study should be considered as an exploratory “proof of principle” rather than a full-fledged rehabilitation study. Future studies should further investigate the issue by including larger samples and applying follow-up measurements. It would also be useful to investigate the efficacy of this new combined GMT+WMT treatment in comparison with GMT only. The results of our study also suggest that the effects of GMT+WMT are more evident on real-life executive tasks. Therefore, when implemented in clinical practice this new treatment should be prevalently assessed in terms of its beneficial outcomes on more ecologically valid measures that involve everyday executive functioning. Future studies are also needed to assess the generalization of this new treatment and the transfer of the acquired skills to other untrained multistep tasks, like ‘using an electronic device’ or ‘setting the car alarm on’. Finally, another future aim could be to integrate this treatment in a larger, more comprehensive treatment (like Spikman’s multifaceted training based on GMT and Problem Solving Training) with the aim to investigate the effects of an extensive treatment.

Conclusion

The studies described in this thesis have investigated the relation between daily executive difficulties (mainly faced by patients with traumatic brain injury), and anterior brain damage. The results indicate that everyday severe executive dysfunction can be attributed to impairments in core executive domains related to primary anterior brain pathology. The conclusions may have considerable clinical implications. They indicate the key executive areas that a clinical neuropsychologist (and other clinicians) should focus on when assessing and treating specific executive difficulties faced by patients with moderate to severe traumatic brain injury in ill-structured complex activities of daily living. Finally, the newly proposed treatment of Goal Management Training and Updating Working Memory provides promising evidence for the improvement of sustained and serial-order behaviour in brain-damaged patients with executive problems in real-life tasks.
References


Evans, J. J., Chua, S. E., McKenna, P. J., & Wilson, B. A. (1997). Assessment of the dysexecutive syndrome in schizophrenia. Psychological Medicine, 27, 635–646.


Summary in English
Nederlandse samenvatting
Acknowledgments
Curriculum Vitae
Publications
Summary

Think of yourself when you have to plan a flight abroad and all the things that have to be done (first choose the place and time, then the aviation company, booking your tickets, make accommodation arrangements, and, of course, inform your boss about the trip...). Before finding yourself at the airport of destination you will have planned and accomplished a vast number of actions. Our abilities to plan and organize complex everyday activities entailing multiple steps (subgoals) demand goal-directed behaviour and higher cognitive functions that are called executive functions. These cognitive functions can be impaired after brain damage. Dysfunction in executive abilities has been traditionally related to anterior brain pathology (anterior areas of the brain are called frontal lobes), even though, nowadays, with the advances of brain-imaging technology, it is well-known that damage to non-anterior regions can also lead to executive dysfunction. However, the nature and extent of executive dysfunction caused after damage to the anterior or non-anterior brain regions has been a challenging issue for research. For example, the ability to plan a route, in which I have to visit several places, presupposes my ability to adequately perceive, attend to and organize visual-spatial information, an ability strongly related to posterior brain areas. However, this ability can be an essential component in the “central” (anterior) executive plan. An additional issue concerns the methods we use to assess deficits in executive abilities after brain damage. Neuropsychological testing (administration of tests sensitive to measure these difficulties) is the usual procedure we follow to obtain an accurate picture about a patient’s functional profile.

Older and more traditional neuropsychological executive tests are more ‘laboratory’ based, and, thus, are applied in the more ‘controlled’ conditions of a clinician’s office. These tests have been found to be sensitive to determine the nature and the severity of anterior brain pathology, even though, this sensitivity has been recently questioned. Nevertheless these conventional tests are not able to capture the specific executive difficulties that a patient with moderate traumatic brain injury (TBI; mostly affecting anterior brain areas) may have in everyday life. Many patients with moderate TBI (and prominent anterior pathology) exhibit good performance on traditional executive tests, whereas, they do not perform well on multistep everyday activities that are more “open-ended” and not so “controlled” by the examiner. This means that these tests lack ‘ecological” validity, in other words they cannot predict difficulties in everyday life.

This has led to the development of new executive tasks that are more ecologically valid and resemble real-life tasks. These tests can help the examiner to detect a patient’s difficulties in tasks that are more “open-ended”. However, these ecologically valid tests have not been systematically investigated so far for their sensitivity to detect the nature and severity of executive dysfunction in patients with anterior brain
pathology. This would be helpful for the accurate assessment of the everyday difficulties of patients with primary damage to the anterior brain regions. It would also facilitate the design of cognitive treatments for the management of executive difficulties in daily life.

**Ecologically valid tasks and their relation to anterior pathology**

This was the topic of exploration in the second chapter of this PhD. thesis. Our aim was to investigate the relation between executive deficits in ecologically valid executive tasks and anterior pathology. For this reason, we used a well-known executive test, the Behavioural Assessment of Dysexecutive Syndrome (BADS) and examined its sensitivity to capture real-life executive deficits related to anterior brain damage. To do so, we recruited two separate patient groups with circumscribed brain lesions, one of 30 patients with anterior lesions and another of 22 patients with posterior lesions and investigated the BADS ability to differentiate between these lesions. Our findings demonstrated that the group of patients with anterior lesions exhibited significantly worse performances than those with posterior lesions in the BADS subtests that demand **cognitive flexibility**, **set shifting**, **action planning**, **intentionality** and **inhibition**. These findings suggest a strong relation between these specific executive problems in real-life tasks and anterior brain damage.

As an extension of the previous study, in chapter 3 our aim was to investigate the sensitivity of a questionnaire that measures the frequency (and thus the severity) of dysexecutive symptoms in everyday living, that is the DEX-Questionnaire. For this purpose, the aforementioned two separate groups of patients (30 patients with anterior and 22 with posterior lesions) were also recruited for the current study. The DEX-Questionnaire was completed by the patients themselves and by their therapists. We found no significant differences between the self-reports of patients with anterior brain damage and those of patients with posterior lesions. On the other hand, the frequency of daily dysexecutive symptoms, as reported by the therapists of the two patient groups, was found to be significantly higher for the patients with anterior lesions than for the patients with posterior lesions. These findings confirm the close relation between daily dysexecutive symptoms and anterior pathology. Additionally, the discrepancy between the self-reports of the patients with anterior lesions and the reports provided by their therapists highlights the lack of self-awareness that characterizes the patients with anterior damage. The DEX-reports of the therapists were also significantly correlated with the patients' dysexecutive performance on the BADS subtests. The strongest relation was found between the DEX-reports of the therapists and the Modified Six Elements Test, a BADS subtest that demands motivation and willingness to purposefully initiate an activity, the inhibition of irrelevant information and actions, the ability to actively retain in memory the several components of a complex activity during its execution, i.e. working memory, and the ability to
monitor and manage time. These findings, consistent with those of our previous study, indicate the sensitivity of the DEX, a behavioural executive questionnaire, to adequately identify anterior pathology. They also suggest that the frequency of the daily dysexecutive symptoms, as measured by the DEX, is related to deficient performance on several core executive functions.

Difficulties in planning and performing multistep activities of everyday living are core executive symptoms as well. A good example of an every task that assesses these impairments is the generation of daily scripts. Script generation entails the verbal description of steps required (in the right order) to successfully perform a script. Thus, in chapter 4, we administered a script generation task to the same participants. This Everyday Description task was aimed at investigating the relation between deficient performance on script generation and anterior pathology. Moreover, the correlation between difficulties in script generation and deficits in specific executive functions was studied. Our results confirm the strong relation between difficulties in script generation and anterior damage. Also, a significant association between poor performance on script generation and dysfunction in core executive domains such as planning, working memory, response generation, inhibition and shifting was found.

Rehabilitation of executive dysfunction after brain damage
Besides the assessment of executive dysfunction in everyday life in patients with anterior pathology, another important issue is the treatment of their executive difficulties in planning and organizing everyday activities that demand the accomplishment of multiple sub-goals. An effective treatment for these impairments is the Goal Management Training (GMT). GMT focuses on teaching patients to systematically use an algorithm consisting of self-instructions and self-monitoring. Based on this "guide", patients are taught to divide multistep tasks into smaller separate steps (sub-goals). They have to learn these steps in the correct order and, following the execution of each step, "stop and check" their successful completion before moving to the next step, until the accomplishment of the main goal. This procedure relies on our ability to sustain attention and to continuously update information in working memory. Patients with brain damage have difficulties in learning and keeping track of the list of subgoals needed for the completion of multi-step everyday tasks. Thus, we thought that a combination of working memory training and Goal Management Training might further improve learning and mental maintenance of step (subgoal) sequences, while executing on-going everyday multistep activities.

Therefore, in chapter 5, we described the rationale and the training protocol of such a combined treatment. Our goal was to facilitate the sequential learning and mental maintenance of on-going steps before the execution of a multistep task. To do
so, we incorporated a visual metaphor (ladder with steps) in one of the stages of Goal management Training. In this stage the patient is required to learn and memorize the sequence of steps. More specifically, the participants were provided with a visual picture (a ladder with steps) and gradually they were asked to imagine this picture without seeing it. We expected that by supporting working memory in keeping steps updated, the execution of the main task would be facilitated.

Chapter 6 describes a treatment study. Herein, we investigated the efficacy of the described treatment by using two main multistep everyday tasks (e.g. how to use the computer to book a theatre-ticket on-line or use the computer to send an e-mail to a friend). This combined treatment was compared to a working memory training designed for other purposes, namely to facilitate the maintenance of information in everyday scenarios (go for shopping, and then pay bills etc.). Therefore we randomly assigned eighteen brain-injured patients with executive deficits to two groups. One group received the new combined treatment, whereas the other group was administered only working memory training. To investigate the efficacy of the new treatment, we compared the performance of these two groups, both on alternative versions of the main multistep tasks and on additional measures. We also conducted pre and post treatment comparisons. Our main finding indicates that the patients in the new treatment performed significantly better than the other patient group. This effect was both found on the alternative versions of the two main multistep real-life tasks as well as on additional executive tasks demanding action planning and maintenance of sequential steps towards the completion of everyday activities. These findings show that the new treatment can significantly facilitate serial-order- and goal-directed behaviour in patients with brain injuries and executive difficulties in real-life multistep tasks.

Finally, in chapter 7, a summary and a discussion of all the empirical chapters is presented. Overall, our main findings indicate that impaired performance on ecologically valid executive tasks reflect deficits in specific domains of executive functioning primarily related to anterior pathology (e.g. intentionality, planning, shifting, inhibition, mental flexibility). Thus, the quantitative and qualitative evidence of poor performance on these tasks can be used as index of real-life executive impairment related to anterior dysfunction. This finding can significantly contribute to a more accurate diagnosis and the formulation of the neuropsychological profiles of patients with brain injuries, as well as to the management of their everyday living problems. Finally, we have shown that a combined treatment, incorporating strategies aimed at facilitating working memory performance and persistence in everyday tasks, may have positive effects on the everyday functionality of these patients.
Nederlandse samenvatting

Denk even aan uzelf als u van plan bent een buitenlandse vlucht te boeken en aan alle dingen die u daarvoor moet doen (tijd en bestemming zoeken, een vliegmaatschappij kiezen, tickets boeken, een hotel reserveren, en vanzelfsprekend uw werkgever op de hoogte brengen dat u afwezig zal zijn). Voor u op de luchthaven van bestemming bent heeft u al een aanzienlijk aantal handelingen gepland en uitgevoerd. Onze vaardigheid om complexe alledaagse taken te plannen en te organiseren vraagt om doelgericht gedrag en hogere cognitieve processen die onder de noemer executieve functies vallen. Deze cognitieve functies kunnen na hersenletsels een aanzienlijke rol spelen. Een aantasting van deze executieve vaardigheden is decennialang gekoppeld geweest aan beschadigingen in de voorste (of anterieure) delen van de hersenen (de frontalklamer). Hedentendage is, onder andere door de vooruitgang van beeldvormende technieken, bekend dat letsels van niet-frontale hersengebieden ook kunnen leiden tot executief disfunctioneren. Echter, de aard en de omvang van de executieve disfuncties veroorzaakt door deze letsels is nog steeds een uitdaging voor wetenschappelijk onderzoek. De vaardigheid om een route te plannen teneinde meerdere bezienswaardigheden te bezoeken, veronderstelt bijvoorbeeld de adequate waarneming van visueelruimtelijke informatie, voldoende aandacht en de organisatie van deze informatie, allemaal vaardigheden die gekoppeld zijn aan posterieur hersengebieden. Niettemin kan deze vaardigheid een essentiële component zijn van een “centraal” (anterieur gelocaleerd) executief plan. Een andere belangrijk probleem vormen de methoden die gebruikt worden om executieve functies in kaart te brengen. Neuro-psychologisch testonderzoek is de gebruikelijke procedure om een accuraat beeld te krijgen van de executieve vermogens van de persoon met een hersenbeschadiging.

De klassieke executieve tests die hiervoor gebruikt worden zijn vaak op laboratoriumtaken gebaseerd en worden bijgevolg toegepast in de meer gecontroleerde en gestructureerde omgeving van de clinicus. Deze testen zijn voldoende sensitief om de aard en de ernst van anterieur hersenpathologie te bepalen. Echter, deze conventionele testen zijn niet in staat om de specifieke executieve problemen te onderkennen die mensen met een traumatisch hersenletsel (vaak met anterieur beschadigingen) in het dagelijks leven ondervinden. Veel patiënten met een matig ernstig traumatisch hersenletsel (en anterieur schade) presteren binnen normale grenzen op deze traditionele executieve testen, terwijl ze toch afwijkingen laten zien op minder afgebakende taken in het dagelijks leven. Dit betekent dat deze tests ecologische validiteit missen; met andere woorden ze zijn niet in staat om problemen in het dagelijks leven te voorspellen.

Dit probleem heeft geleid tot de ontwikkeling van nieuwe executieve testen met een betere ecologischevaliditeit, die meer lijken op taken uit het dagelijks leven. De sensitiviteit van deze testen om de aard en de ernst van het executief disfunctioneren
bij patiënten met anterieure letsels te detecteren is echter niet uitgebreid onderzocht. Met dergelijke taken kunnen de problemen in dagelijkse executieve taken beter vastgesteld worden bij patiënten met anterieure letsels en aanknopingspunten voor effectieve behandelingen gevonden worden.

**Ecologisch valide taken en hun relatie met anterieure pathologie**

Dit was het onderwerp van onderzoek in Hoofdstuk 2 van dit proefschrift. Hierin is de relatie onderzocht tussen executieve stoornissen op ecologisch valide taken en anterieur hersenletsel. Daarvoor is de Behavioural Assessment of the Dysexecutive-Syndrome (BADS) gebruikt. De sensitiviteit van deze test voor dagelijkse executieve stoornissen bij patiënten met anterieure hersenletsels is onderzocht. Daarvoor hebben we twee groepen patiënten met welomschreven letsel gerekruiteerd; dertig patiënten met anterieur letsel en 22 patiënten met posterieur letsel. Het vermogen van de BADS om deze twee groepen te onderscheiden is onderzocht. De groep met anterieure leasies presteerde slechter dan de groep met posterieur letsel op een aantal subtests van de BADS gericht op cognitieve flexibiliteit, set shifting, actieplanning, intentionaliteit en inhibitie. De resultaten suggereren ook dat er een sterke relatie aanwezig is tussen specifieke executieve problemen in het dagelijks leven en anterieur hersenletsel.

Een vervolg van deze studie is beschreven in hoofdstuk 3. In dit hoofdstuk is de sensitiviteit van een vragenlijst onderzocht die de frequentie (en dus ook de ernst) van executieve symptomen in het dagelijks leven met, te weten de DEX-vragenlijst. Met dit doel voor ogen hebben we dezelfde patiënten gerekruiteerd als in het vorig onderzoek. De DEX-vragenlijst werd ingevuld door de patiënten zelf en door één van hun therapeuten. Er bleken geen verschillen te zijn tussen de zelfrapportages van patiënten met anterieur en posterieur letsels. De therapeuten gaven echter wel meer executieve problemen aan bij patiënten met anterieur letsel dan bij patiënten met posterieur letsel. Deze resultaten bevestigen de relatie tussen dagelijkse executieve problemen en anterieur hersenpathologie. Bovendien geeft de discrepantie tussen de zelfrapportages van patiënten met anterieure leasies en de rapportages van hun therapeuten aan dat deze patiënten kampen met een duidelijk gebrek aan ziekte-inzicht. De scores op de DEX-vragenlijsten van de therapeuten hingen ook samen met de prestaties van de patiënten op een aantal subtests van de BADS. De sterkste relatie bestond tussen de DEX-rapportages van therapeuten en de Modified Six Elements Test. Deze subtest van de BADS vereist motivatie en de bereidheid om activiteiten te initiëren, naast de vaardigheid om irrelevantie informatie te inhiberen en het vermogen om de verschillende componenten van een activiteit in het werkgeheugen actief te houden. Ook de vaardigheid om de tijd te monitoren en te manipuleren zijn in deze subtest een vereiste. De bevindingen zijn in overeenstemming met de resultaten van hoofdstuk 2 en geven aan dat de DEX-vragenlijst sensitief is om anterieur hersenletsel te identificeren. Ook was de frequentie van
voorkomen van dagelijkse executieve problemen gerelateerd is aan slechte prestaties op meerdere taken die executieve kernfuncties meten.

Problemen met de planning en uitvoering van dagelijkse activiteiten behoren ook tot de executieve kernsymptomen. Een goed voorbeeld van een dergelijke taak is het genereren van scripts. Scriptgeneratietaken vereisen de verbale beschrijving van alle stappen die nodig zijn om een script uit te voeren. In hoofdstuk 4 hebben we een script generatietak voorgelegd aan de participanten van de vorige onderzoeken. Met deze EverydayDescriptionTaskis de relatie tussen problemen met script generatie en anterieure hersenpathologie onderzocht. Ook is de relatie tussen problemen met scriptgeneratie en stoornissen in specifieke executieve functies onderzocht. De resultaten lieten een significante relatie zien tussen afwijkingen in scriptgeneratie en anterieure hersenbeschadigingen. Ook is een significante associatie gevonden tussen afwijkende prestaties in scriptgeneratie en executieve functies zoals planning, werkgeheugen, responsgeneratie, inhibitie en shifting.

De behandeling van executieve disfuncties na hersenletsel
Naast de diagnostiek van executieve problemen is de behandeling van executieve stoornissen ook van belang. Een behandeling voor deze problemen is Goal Management Training (GMT). GMT is erop gericht patiënten met executieve problemen te leren om op een systematische manier een algoritme te gebruiken dat gebaseerd is op zelfinstructie en zelfmonitoring. De “GMT-gids” leert patiënten om taken onder te verdelen in kleinere stappen en subdoelen. Patiënten moeten deze stappen in de juiste volgorde leren toepassen en na de uitvoering van iedere stap een “stop-en controlemoment” inbouwen, om te controleren of de stap is uitgevoerd. Pas daarna wordt de volgende stap onder handen genomen, totdat het hoofddoel bereikt wordt. Deze procedure vereist volgehouden aandacht en het continu updaten van informatie in het werkgeheugen. Patiënten met hersenletsel hebben moeite met het leren en het bijhouden van deze subdoelen en deelstappen. Door het combineren van werkgeheugentraining met Goal Management Training zou het leren en het online beschikbaar houden van stappen en subdoelen verbeterd kunnen worden.

In hoofdstuk 5 de rationale en het trainingsprotocol van een dergelijke combinatietraining beschreven. Het doel van de training was om het sequentieel leren en onthouden van stappen te faciliteren voorafgaand aan de uitvoering van een alledaagse vaardigheid. Daarvoor hebben we een visuele metafoor (een ladder met treden) geïntroduceerd in één van de onderdelen van GMT. In dit onderdeel wordt de patiënt gevraagd om de stappen te leren en in het geheugen op te slaan. Het plaatje van een ladder met treden werd getoond en de patiënt werd gevraagd om dit plaatje geleidelijk te vervangen door een ingebeeld plaatje. Onze verwachting was dat door het werkgeheugen op deze manier te ondersteunen de uitvoering van de taak gefaciliteerd zou worden.
In hoofdstuk 6 is de effectiviteit van de bovengenoemde combinatiebehandeling onderzocht. Hiervoor hebben we twee dagelijkse vaardigheden gebruikt (via computer een theaterkaartje bestellen en een email naar een vriend of vriendin verzenden). De combinatiebehandeling werd vergeleken met een werkgeheugen-training die een ander doel had, namelijk het vasthouden van informatie in alledaagse scenarios (boodschappen gaan doen, daarna rekeningen betalen, etc.). We hebben 18 patiënten met hersenletsel en executieve problemen op basis van toeval toegewezen aan de twee groepen. Één groep kreeg de nieuwe combinatiebehandeling, de andere groep kreeg alleen werkgeheugentraining. Om de effectiviteit van de nieuwe behandeling te onderzoeken hebben we de prestaties van beide groepen op alternatieve versies van de twee genoemde taken en op een aantal andere taken onderzocht. De patiënten in de nieuwe combinatiebehandeling bleken beter te presteren dan de mensen in de andere patiëntengroep. Deze effecten waren niet alleen zichtbaar bij de alternatieve versies van de twee taken, maar ook bij een aantal andere executieve taken die een beroep doen op planning en het vasthouden van sequentiële stappen. Deze bevindingen wijzen er op dat de nieuwe interventie serieel doelgericht gedrag verbetert bij hersenbeschadigde patiënten met executieve problemen in het dagelijks leven.

In hoofdstuk 7 wordt een samenvatting en discussie van alle empirische hoofdstukken gegeven. Geconcludeerd kan worden dat afwijkende prestaties op ecologisch valide executieve taken toegeschreven kunnen worden aan specifieke executieve problemen die primair gerelateerd zijn aan anterieure pathologie (bijvoorbeeld intentionaliteit, planning, shifting, inhibitie en mentale flexibiliteit). Zodoende kunnen de kwalitatief en kwantitatief slechtere prestaties op deze taken gebruikt worden als een indicator voor executieve beperkingen in het dagelijks leven bij patiënten met anterieur letsels. Deze bevinding kan een belangrijke bijdrage leveren aanbetere diagnostiek van patiënten met hersenletsel, alsmede aan de behandeling van hun alledaagse problemen. Ten slotte hebben we laten zien dat een nieuwe interventie positieve effecten heeft op het alledaagse functioneren van patiënten.
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With all my thankfulness and respect,
Anna Emmanouel
**Curriculum Vitae**

Anna Emmanouel was born in 12th November 1978 and grew up in Thessaloniki, Greece. After her graduation from the second high school of Ilioupolis (Thessaloniki, Greece), she took national written examinations and entered the Psychology Department of Aristoteles University, Thessaloniki, Greece (in 1997). Her special interest in brain function and neuropsychology motivated her to attend undergraduate courses in neuropsychology and, after completion of the undergraduate studies (in 2002), to take (again) written examinations and entered the Aristoteles Master Programme in Cognitive Psychology with specialization in Clinical Neuropsychology (in the same year). During her Master studies (2002-2005), she acquired specialized knowledge and extensive practical training (1,683.5 hours of practice in several clinical placements) in the specialty of clinical neuropsychology. She was specifically trained in the assessment and treatment of cognitive impairments after brain damage, especially in adult patients with various diseases of the central nervous system. She started as an external PhD student (in 2008) at the Neuropsychology and Rehabilitation Psychology group of the Donders Institute, Radboud University, Nijmegen, the Netherlands. She also has a seven-year professional work experience (2006-2013) as a clinical neuropsychologist in collaboration with private clinics and rehabilitation centers in Thessaloniki, Greece. Currently, she is working as a part-time lecturer at City College, the International Faculty of the University of Sheffield in Thessaloniki, Greece.
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