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The role of white matter hyperintensities and medial temporal lobe atrophy in age-related executive dysfunctioning

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ABSTRACT

Various studies support an association between white matter hyperintensities (WMH) and deficits in executive function in nondemented ageing. Studies examining executive functions and WMH have generally adopted executive function as a phrase including various functions such as flexibility, inhibition, and working memory. However, these functions include distinctive cognitive processes and not all may be affected as a result of WMH. Furthermore, atrophy of the medial temporal lobe (MTA) is frequently observed in ageing. Nevertheless, in previous studies of nondemented ageing MTA was not considered when examining a relationship between white matter and executive function. The goal of the present study was to examine how WMH and MTA relate to a variety of executive functions, including flexibility, fluency, inhibition, planning, set shifting, and working memory. Strong correlations were observed between WMH and MTA and most of the executive functions. However, only MTA was related to flexibility and set shifting performance. Regression analysis furthermore showed that MTA was the strongest predictor of working memory, after which no further significant association with WMH was noted. Alternatively, both MTA and periventricular hyperintensities independently predicted inhibition performance. These findings emphasize the importance of MTA when examining age-related decline in executive functioning.

1. Introduction

Normal ageing is associated with a decline in cognitive functions, including executive function (Keys & White, 2000; MacPherson, Phillips, & Della Sala, 2002). White matter hyperintensities (WMH), indicative of reduced white matter integrity, are frequently observed in ageing and might mediate the decrement in executive function (e.g. O'Sullivan et al., 2001). The white matter forms the cortico–cortical and cortico–subcortical connections and is important for functioning of the prefrontal cortex (PFC), a brain area that is extensively connected to both cortical and subcortical regions (Pandya & Yeterian, 1996). This functional connectivity of the PFC implies a central role for the PFC in the integration of various cognitive functions, which is crucial for executive function (Royall et al., 2002). By reducing the functional connectivity of the PFC with other (sub-)cortical regions, WMH have been found to induce deficits in executive function (Marshall, Hendrickson, Kaufer, Ivanco, & Bohnen, 2006; O'Brien et al., 2002; O'Sullivan et al., 2001).

Although an association between WMH and a decline in executive function has been well established, several issues regarding this relationship require elucidation. The term executive function has been used as a single construct including a variety of functions such as working memory, inhibition, and flexibility. Previous studies mostly focused on a single or only a few tests as representative of the entire executive function domain (e.g. Baum, Schulte, Girke, Reischies, & Felix, 1996; Gunning-Dixon & Raz, 2003; Marshall et al., 2006; Shenkin et al., 2005). Moreover, whether all executive functions are affected by WMH remains indefinite. For example, findings regarding the relationship between WMH and flexibility, measured with the Trail Making Test part B (TMT-B), or fluency performance, are inconsistent (Bartres-Faz et al., 2001; Baum et al., 1996; DeCarli et al., 1995; Dufouil, Alperovitch, & Tzourio,

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2003). Whether planning, another executive function that is strongly affected by ageing (Andres & Van der Linden, 2000; Phillips, Kliegel, & Martin, 2006; Robbins et al., 1998), relates to WMH in the aged population is unclear. Set shifting performance constitutes another function within the executive domain where varying results with regard to WMH-related decline in task performance have been reported (Boone et al., 1992; Gunning-Dixon & Raz, 2003; Oosterman, Sergeant, Weinstein, & Scherder, 2004; Raz, Rodrigue, & Acker, 2003; Schmidt et al., 1993, 1995).

Next to WMH, mild atrophy of the medial temporal lobe (MTA) is observed in ageing (Raz, Rodrigue, Head, Kennedy, & Acker, 2004; Yonelinas et al., 2007). The medial temporal lobe is well known for its role in episodic memory. Next to the typical involvement in memory and learning, however, it is known that interactions between the medial temporal lobe, including the hippocampus, and prefrontal brain areas exist (Laroche, Davis, & Jay, 2000). Although traditionally referred to as a medial temporal lobe function, previous studies do point to an involvement of the PFC and of executive function in memory performance (e.g. Ranganath, Johnson, & D'Esposito, 2003; Rossi et al., 2006; Simard, Rouleau, Brosseau, Laframboise, & Bojanowsky, 2003). Furthermore, indirect projections of the PFC, through the thalamus, to the hippocampus have been identified in rats (Vertes, Hoover, Szigeti-Buck, & Leranth, 2007). Functional connectivity between the PFC and medial temporal lobe has been suggested by previous studies showing an excitatory effect of hippocampal activity on PFC functioning (Laroche et al., 2000). This implies that the medial temporal lobe may be involved in functions characteristic of the prefrontal cortex, including executive functions. Confirmative of this idea, MTA has been related to a decrease in fluency ability, a test of executive function, in an aged study sample that included demented subjects (Launer et al., 1995). Similarly, another study reported MTA to predict executive functioning in patients with mild cognitive impairment (van der Pol et al., 2007). Final evidence for involvement of the medial temporal lobe in executive function comes from a study showing a direct association between these functions and dopamine D2 receptor binding in the hippocampus (Takahashi et al., 2007). One possible rationale for these observations focuses on the multidisciplinary nature of executive functions and the tests employed to measure them. The term 'executive function' refers to the "high-order functions operating in non-routine, i.e. novel, complex, and/or conflicting situations" (Godefroy, 2003). In order for these functions to operate necessitates the integration of diverse cognitive functions. This indicates that intact executive functioning is partly dependent on other cognitive functions, such as memory. Indeed, previous studies point to a role of memory performance in executive function tasks (e.g. Giovagnoli, 2001). The medial temporal lobe is a structure highly important for memory. Therefore, by affecting memory functions, MTA may also induce a deficit in executive function.

The present study focuses on several issues. First of all, the relationship between WMH and various executive functions (i.e. flexibility, fluency, inhibition, planning, set shifting, working memory) will be assessed. As WMH induces cortical disconnection, an inverse relationship between WMH and all executive functions is expected. Secondly, the effect of MTA will be examined and taken into account with regard to the relationship between executive functions and WMH. Reduced integrity of the medial temporal lobe, affecting connectivity with the prefrontal cortex and the presumed involvement in executive functions, is expected to also inversely relate to executive performance. Although interconnected, the functions of the PFC, which are impaired by WMH, include different ones from those exerted by the medial temporal lobe (Sloan, Good, & Dunnett, 2006). Therefore, a complementary relationship between WMH and MTA in task performance is expected.

2. Methods

2.1. Subjects

One hundred and sixty subjects participated. The recruitment of participants for this study was accomplished in cooperation with the Sint Lucas Andreas Hospital in Amsterdam, The Netherlands. The selection procedure of the subjects was as follows. Ageing poses the major risk for WMH (Ylikoski et al., 1995), and since white matter volume starts declining during the fifth decade of life (Bartzokis et al., 2001; Walhovd et al., 2005), age was restricted to a minimum of 50 years for inclusion. As this study is part of a larger study focusing on cardiovascular risk factors, medical records of elderly people visiting the outpatient clinic (e.g. of cardiology or internal medicine) were screened to select subjects with and without these risks. As such, most subjects (83.1%) had one or more of these risks, including a history of hypertension, hypercholesterolemia, diabetes mellitus, cardiovascular disease (myocardial infarction, congestive heart failure, coronary artery disease, atrial fibrillation), and smoking. These risk factors have been acknowledged as risks for WMH and MTA (Den Heijer et al., 2003, 2005; Jeerakathil et al., 2004; Lazarus, Prettyman, & Cherryman, 2005). A small percentage of participants (16.9%) consisted of healthy partners or neurological out-patients visiting the hospital for low back pain or a peripheral nerve problem; all were without a history of cardiovascular risk factors and all fulfilled the age criterion.

A prerequisite for subjects to participate was to be free of a history of neurodegenerative disease (e.g. dementia, Parkinson's disease), stroke, alcohol or other substance abuse, or psychiatric disease. Furthermore, the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) was used as a screening instrument to exclude possible dementia: a score of $\geqslant 26$ was required for participation. Both premorbid IQ, assessed with the Dutch version of the National Adult Reading Test (Schmand, Bakker, Saan, & Louman, 1991) and education, assessed with an ordinal rating scale ranging from 1 (incomplete primary school) to 7 (university degree) (Heslinga, van den burg, & Saan, 1983), were measured. Using standardized z-scores, a single composite was calculated representing intelligence. Subject details are presented in Table 1. Approval for this study was obtained from the Sint Lucas Andreas medical ethics committee. All subjects signed an informed consent form.

2.2. Executive functions

The neuropsychological battery completed by the participants consisted of tests measuring the following executive functions: flexibility, fluency, inhibition, planning, set shifting, and working memory. A single score, using standardized z-scores, was calculated for each executive function. Scores were adjusted such that a higher score always represented better performance.

2.2.1. Flexibility

The Trail Making Test (TMT; Reitan, 1958) was employed to assess flexibility performance. The TMT-A consists of 25 encircled

Table 1
Subject characteristics ($N = 160$)

Variable	Value
Age (mean ± SD)	68.3 (8.7)
Sex (% male)	61.3
Education (mean ± SD)	4.5 (1.5)
IQ (mean ± SD)	99.9 (13.5)
MMSE (mean ± SD)	28.1 (1.4)

MMSE, Mini mental state examination.

numbers that are randomly distributed on a sheet of paper. The subject is required to sequentially connect these numbers. With the TMT-B, both numbers and letters are distributed. This time, the subject is instructed to alternate between the numbers and letters (e.g., 1, A, 2, B, 3, etc.). Completion time of part B corrected for part A (TMT-B/TMT-A) and TMT-B number of errors were considered.

2.2.2. Fluency

Both Category Fluency and the Controlled Oral Word Association Test (COWAT; Benton, Hamsher, & Sivan, 1983) were administered. Subjects are instructed to generate as many words as possible within 1 min. For Category Fluency total number of words of 'animal' and 'profession' categories is noted. The COWAT score consists of the total number of words beginning with a specific letter (Dutch equivalent of 'fas').

2.2.3. Inhibition

Both the Colour (C) and Colour/Word (C/W) cards of the Stroop test (Stroop, 1935) were administered. For the C card, 10 rows, with each row containing 10 coloured blocks are presented, and the subject is required to name the colours of the blocks as fast as possible. On the C/W card, instead of coloured blocks, colour names are printed in an incongruent colour, and the subject is required to name the colours in which the words are printed. Completion time of the C/W card corrected for the C card (time C/W−time C) and the number of errors on the C/W card were registered.

2.2.4. Planning

Stockings of Cambridge (CANTAB), a computerized version of the Tower of London test, was used to assess planning ability. Two displays with coloured balls are presented, and subjects have to adjust one display so that it matches the other one in a minimal number of moves (ranging from 2-step problems to 5-step problems). The subject is instructed to first think about the moves to be performed before starting moving the coloured balls. A maximum number of moves (5, 7, 9, and 12 moves for 2, 3, 4, and 5-step problems, respectively) is allowed before the trial terminates and the next problem is introduced. The number of problems solved in minimal moves was noted.

2.2.5. Set shifting

The Intra/Extra Dimensional Set Shifting (CANTAB) test was employed to measure set shifting ability. The test starts with the presentation of four boxes in which two stimuli (shapes) are displayed, one correct and one incorrect. The subject has to find out which of the two shapes is the correct one and, once found, has to continue choosing the 'correct shape' (stage 1). When the computer establishes full comprehension of the rule (after six successive correct trials), the rule is changed (the previous incorrect shape is now correct, stage 2). Successful comprehension induces stages 3 and 4, in which irrelevant information (white lines displayed, respectively, next to and superimposed on the shapes) that must be ignored is additionally presented. In stage 5 a shift towards the other shape is required. In stage 6 an intradimensional shift is initiated, with novel stimuli but the same principle (shapes remain the correct dimension). A reversal to the alternate shape is required in stage 7. Finally, in stage 8 novel stimuli are presented but this time an extradimensional (ED) shift towards the white lines is required. Successful completion of this stage induces a shift to the opponent line (stage 9). When a stage is not completed after 50 consecutive trials, the test terminates. In case a subject fails to complete a stage prior to stage 9, a total of 25 errors is noted for each following uncompleted stage. This test is about set shifting and rule generation, and the ED shift has frequently been denoted as a computerized version of the Wisconsin Card Sorting Test. Number of stages completed and the number of errors needed to complete the ED shift (ED errors) were of interest.

2.2.6. Working memory

The Spatial Working Memory test (CANTAB) was included to examine working memory. In this test several boxes are displayed, in one of which a blue token is hidden. Subjects have to search for this token and, once found, collect it in an empty space on the right side of the screen. Each time a token has been found, a new token is hidden. Subjects are instructed that once a token was found, that particular box would never be used again to hide a token. Two different outcome measures as representatives of working memory function were of interest. The first was the number of 'between errors', which represents the number of times subjects re-opened a box where a blue token had already been discovered in during that search trial. Secondly, the number of 'within errors' was calculated which represents the number of times a subject re-opens a previously examined box within a single search sequence.

2.3. MRI data

A 1.5 Tesla scanner was used to obtain brain MRIs (GE-Signa Horizon LX). A standardized imaging protocol consisting of sagittal T1-weighted (repetition time TR 300 ms, echo time TE 4 ms) and axial T2-weighted (TR 6500 ms, TE 105 ms) and axial and coronal fluid attenuated inversion recovery (FLAIR) weighted images (TR 10,000 ms, TE 160 ms) was acquired.

The degree of WMH was rated according to a highly validated semiquantative visual rating scale (Scheltens et al., 1993). The interrater weighted Cohen's kappa's was >0.85 (against an internally established gold-standard). Periventricular hyperintensities (PVH) were examined in three regions, frontal and occipital caps and periventricular bands, and rated on a three-point scale: none (score 0); 5 mm or less (score 1); 6–10 mm (score 2). The deep white matter hyperintensities (DWMH) were examined in four regions of the brain, the frontal, parietal, temporal, and occipital lobes, and were rated as follows: none (score 0); less than 4 mm and five or less lesions (score 1); less than 4 mm and six or more lesions (score 2); 4–10 mm and five or less lesions (score 3); 4–10 mm and six or more lesions (score 4); 10 mm or greater and one or more lesions (score 5); and large confluent lesions (score 6). Total PVH and DWMH scores were used for the analyses. In addition, a visual rating scale was employed to evaluate MTA (possible range of scores for each side is 0–4, with higher scores indicating increasing levels of MTA) (Scheltens et al., 1992). Average score of left and right MTA was used for the analyses.

2.4. Statistical analyses

All variables were checked for normal distribution; violations of normality were subjected to Blom transformation.

Partial correlations between the executive functions, white matter variables and MTA were calculated, controlling for gender and the intelligence score, in order to examine the relationship between executive functions, white matter and MTA.

To determine the unique contributions of the white matter scores and MTA to executive functions, hierarchical multiple regression analyses with stepwise selection were performed while controlling for gender and intelligence. Significance for entry was set at $p < .05$.

3. Results

Of the 160 subjects initially enrolled into the study, an MRI-scan was not obtained for 9 subjects. As such, 151 subjects were included in the analyses.

3.1. White matter hyperintensities, medial temporal lobe atrophy, and executive functions

Correlations between the executive functions, white matter variables and MTA are presented in Table 2. Fluency performance was not correlated with any of the MRI variables. A significant correlation was observed between flexibility performance and MTA ($r = -0.21$, $p < .05$). Inhibition functions correlated significantly with PVH ($r = -0.23$, <.01) and with MTA ($r = -0.23$, <.01). Working memory performance was significantly related to MTA ($r = -0.23$, <.01) and to PVH ($r = -0.17$, <.05). Set shifting revealed a significant correlation with MTA ($r = -0.20$, $p < .05$). Finally, planning ability correlated with DWMH ($r = -0.17$, $p < .05$).

Results from the hierarchical multiple linear regression analyses are displayed in Table 3. Conform the results of the correlational analysis, MTA but none of the white matter variables predicted flexibility ($\beta = -0.19$, $p < .05$) and set shifting ($\beta = -0.19$, $p < .05$) functions. MTA entered as the strongest predictor of inhibition performance ($\beta = -0.15$, $p < .05$), after which PVH entered as well ($\beta = -0.15$, $p < .05$). Furthermore, after MTA entered the analysis as a predictor of working memory ($\beta = -0.22$, $p < .01$), none of the white matter variables significantly related to this executive function. Finally, DWMH was the sole predictor of planning ability ($\beta = -0.16$, $p < .05$).

3.2. Frontal white matter hyperintensities

Previous studies suggest a specific involvement of frontal WMH in age-related executive dysfunctioning (Brickman et al., 2006; Gunning-Dixon & Raz, 2003). In order to test this possibility, percentage of frontal (frontal PVH + frontal DWMH) and non-frontal (all other white matter regions) white matter hyperintensities was calculated (this was accomplished by dividing the rated WMH score by the total WMH score possible for these regions). Multiple regression analyses with a stepwise procedure were repeated, only this time MTA, frontal WMH, and non-frontal WMH were selected as independent variables.

Overall, results were comparable to previous findings; MTA was the only predictor of flexibility, working memory, and set shifting behaviour. Frontal WMH were most important with regard to planning ability. Finally, MTA, but this time none of the WMH scores, predicted inhibition performance.

4. Discussion

This paper addresses several issues regarding the relationship between various executive function tests, WMH, and MTA in ageing.

Table 2
Correlations between executive functions, white matter hyperintensities, and medial temporal lobe atrophy

Executive function	MRI variable		
	PVH	DWMH	MTA
Flexibility	−0.14	−0.10	−0.21*
Fluency	−0.07	−0.07	−0.12
Inhibition	−0.23**	−0.11	−0.23**
Planning	−0.14	−0.17*	−0.13
Set shifting	−0.01	−0.10	−0.20*
Working memory	−0.17*	−0.12	−0.23**

Correlations between executive functions, PVH, DWMH, and MTA are displayed while controlling for gender and intelligence.
DWMH, deep white matter hyperintensities; MTA, medial temporal lobe atrophy; PVH, periventricular hyperintensities.
* $p < .05$.
** $p < .01$.

Table 3
Predictive values of white matter hyperintensities and medial temporal lobe atrophy for executive functions

	Executive functions					
	Flexibility (β)	Fluency (β)	Inhibition (β)	Planning (β)	Set shifting (β)	Working memory (β)
Covariates						
Intelligence	0.35***	0.63***	0.46***	0.29***	0.32***	0.27***
Gender	0.03	0.01	−0.14	−0.13	0.07	−0.15
MRI variables						
PVH	–	–	−0.15*	–	–	–
DWMH	–	–	–	−0.16*	–	–
MTA	−0.19*	–	−0.15*	–	−0.19*	−0.22**

Hierarchical multiple regression analyses were performed, controlling for gender and intelligence. PVH, DWMH, and MTA were subjected to a stepwise selection procedure. β coefficients are only reported for those variables that entered the analysis.
DWMH, deep white matter hyperintensities; MTA, medial temporal lobe atrophy; PVH, periventricular hyperintensities.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

First of all, associations were noted between WMH and the following executive functions: inhibition, planning, and working memory. Whereas inhibition and working memory performance were related to PVH, planning ability correlated with DWMH. MTA revealed significant correlations with the majority of the executive functions, including flexibility, inhibition, working memory, and set shifting performance. Further analyses indicated that MTA and PVH (in that order) were both independent predictors of inhibition performance. DWMH was the sole predictor of planning functions. MTA entered as the strongest predictor of working memory performance, after which the relationship between PVH and working memory was no longer significant. Finally, only MTA could significantly contribute to flexibility and set shifting performance. With the exception of planning ability, no specific association between task performance and frontal white matter was noted. To summarize, a unique association was observed between PVH and inhibition and between DWMH and planning performance, whereas MTA related to flexibility, inhibition, working memory, and set shifting.

Previous literature with regard to WMH suggests that the periventricular white matter may be most important for executive function (e.g. De Groot et al., 2000; Van den Heuvel et al., 2006; Ylikoski et al., 1993). These studies, however, mostly examined the Stroop test as a measure of executive function. Our study is in agreement with these results, considering the strong association that was noted between inhibition performance, measured with the Stroop test, and PVH. Yet, besides a correlation with working memory, no association between PVH and other executive functions was noted. DWMH was furthermore the only predictor of planning functions

Interestingly, both flexibility and set shifting performance related to MTA, but not WMH. For flexibility performance, as assessed with the TMT-B, a specific role of the temporal lobe in task performance has been implicated (Zakzanis, Mraz, & Graham, 2005), which might explain the involvement of MTA in flexibility performance in the present study. Also, medial temporal lobe volume has been found to relate to TMT-B performance in a study sample consisting of subjects who were either non-demented, demented, or diagnosed with mild cognitive impairment (van der Flier et al., 2005). Furthermore, a previous study revealed a specific association between hippocampal sclerosis and impaired performance on the Wisconsin Card Sorting Test, a test comparable to the set shifting test employed in the current study (Giovagnoli,

2001). A similar observation was made by Corcoran and Upton (1993), who found a strong association of hippocampal sclerosis with specifically Wisconsin Card Sorting Test performance, but a less pronounced association with fluency and inhibition performance. These studies point to a specific relationship of the medial temporal lobe with flexibility and set shifting performance.

Next to the association with flexibility and set shifting, MTA was an independent predictor of inhibition and working memory performance. This implies an important role of MTA in age-related decline in executive functions in the present study. A following question regards the exact nature of this relationship, considering the traditional role for memory and learning that has been assigned to the medial temporal lobe. However, it has been argued that viewing the hippocampus solely in relation to episodic memory might be inappropriate (Barr & Goldberg, 2003). Connections between this structure and the prefrontal cortex (Barbas, 2000; Laroche et al., 2000) as well as studies implying a role between the hippocampus and executive functions (e.g. Takahashi et al., 2007) suggest that, when examining executive functions, the role of the medial temporal lobe should be considered. More specifically, a reduction in working memory performance as a result of MTA might account for the current observations (Hartman, Bolton, & Fehnel, 2001; Hartman, Steketee, Silva, Lanning, & Andersson, 2003). Previous studies point to the importance of the prefrontal-hippocampal circuit with regard to working memory performance. This implies that diminished functioning of this circuit, as a consequence of MTA, results in decreased working memory performance and hence impaired executive functions. The observation of disrupted working memory performance following disconnection of this circuit in rats supports this postulation (Wang & Cai, 2006). The involvement of memory in tests of executive functions has been suggested previously. For example, initial learning of rules might be one of the 'medial temporal lobe processes' important for successful set shifting performance (Giovagnoli, 2001). Similarly, a role of working memory in the TMT-B performance has been suggested (Zakzanis et al., 2005), probably in keeping track of the encountered numbers and letters. To summarize, a reduction in working memory performance might account for the currently observed associations between MTA and executive functions.

One issue that remains unspecified concerns the precise role of the various structures that make up the medial temporal lobe, including the hippocampal formation, amygdale, and the entorhinal, perirhinal, and parahippocampal cortices. Previous studies point to a specific hippocampal-prefrontal connectivity (Barbas, 2000; Laroche et al., 2000), involvement of the hippocampus in declarative memory, and a specific relationship between the hippocampus and executive functions (e.g. Giovagnoli, 2001). Although it is well recognised that the other medial temporal lobe structures are important for declarative memory functioning and do project to the orbitofrontal and medial prefrontal cortex (Barbas, 2000), it is unclear how and whether these structures relate to EF. One plausible possibility is that, considering the functional and anatomical connectivity between these medial temporal lobe structures (Preston & Gabrieli, 2002), the integrity of the medial temporal lobe as a whole is important for executive functions.

A possible limitation of the present study includes the use of visual rating scales instead of automated volumetric assessments of WMH and MTA. However, several studies do reveal comparable results between visual and volumetric assessments of WMH (Kapeller et al., 2003; van Straaten et al., 2006), also with respect to their relationship with cognition (Gouw et al., 2006). A similar observation was made with regard to MTA, in which the same scale as applied in the present study showed good agreement with volumetric ratings (Bresciani et al., 2005), supporting the use of these visual rating scales in the present study.

One point that warrants caution is that, although several significant associations were noted between WMH, MTA, and executive function, most of these associations were quite small. MTA and WMH could only account for part of the variation in test performance, implying that other factors are involved here. However, the observed associations were not due to cardiovascular risk factors or depressive symptoms (data not shown), indicating the robustness of the current observations.

The present study provides more insight into the relationship between executive functions and WMH, and how MTA is involved in this association. Considering the association between white matter and only some of the executive functions, it can be argued that when examining an age-related decline in executive functions, it is crucial to differentiate between the various functions that comprise the executive domain. Furthermore, MTA may play a very important role with regard to executive functioning in this population.

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