Executive functions

Definition: Executive functions are considered to be the highest-level functions that exert control over more elementary processes. Executive processes are involved in the planning and allocation of attentional resources to ensure that goal-directed behaviour is initiated, maintained and monitored adequately to achieve goals. They include action initiation and inhibition, planning, execution of sequences, set-shifting and maintenance, and verification. **Executive functions include verbal reasoning, problem-solving, planning, the ability to maintain sustained attention, resistance to interference, multitasking, cognitive flexibility, and the ability to cope with novelty.**

Executive functions engagement is prominent particularly in non-routine situations such as novel, conflicting or complex tasks or in routine situations where self-activation is required to optimize efficiency. These control processes also call on working memory, decision-making and **attentional processes**. Three general functional divisions within the domain of attention can be identified: alerting, spatial orienting, and executive control.

Figure 1: Example of a non-routine task in a visual matching task using the unconventional view task condition (Nemcova-Elfmarkova et al., 2017)

N. Nemcova Elfmarkova et al. — *Neuropsychologia 106 (2017) 236–244*

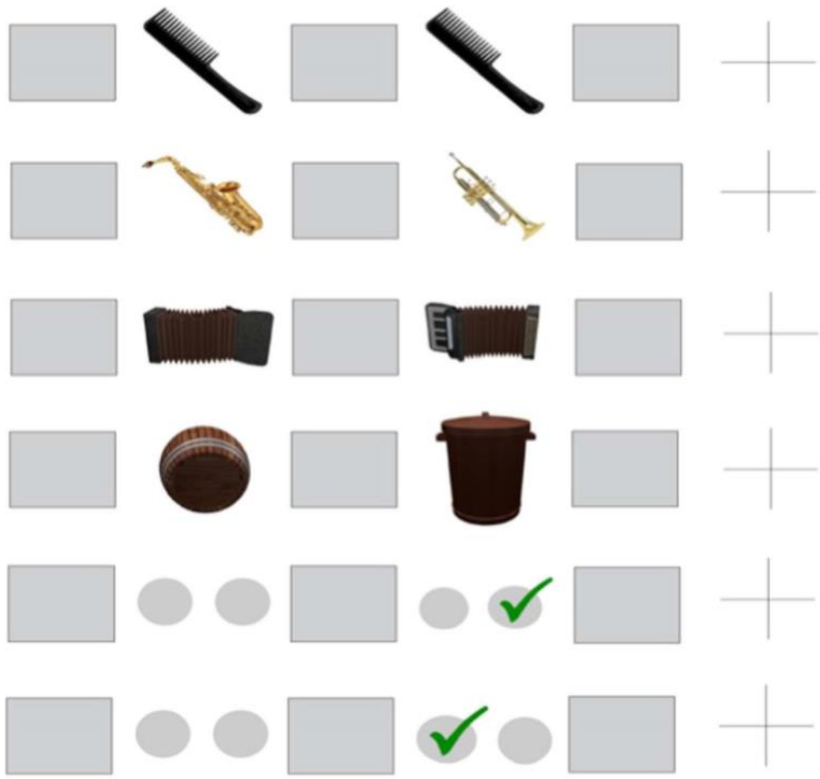


Fig. 1. Visual matching task using conventional and unconventional views of object pairs and the control task. Line 1: Conventional view task condition; the correct answer is YES (left button), Line 2: Conventional view task condition; the correct answer is NO (right button), Line 3: Unconventional view task condition; the correct answer is YES (left button), Line 4: Unconventional view task condition; the correct answer is NO (right button), Line 5: Control task condition (right button), Line 6: Control task condition (left button).

By using this task, Nemcova-Elfmarkova et al. (2017) demonstrated that both MCI-PD (mild cognitive impairment due to PD) and MCI-AD (mild cognitive impairment due to AD) groups performed worse than age-matched controls in the unconventional views condition and showed reduced activation of right anterior cingulate cortex and right superior parietal lobule (PD with MCI), and right middle and inferior frontal gyri (MCI due to AD). Neural responses in cortical areas within the ventral and dorsal visual pathway appeared to be preserved in both MCI groups. Impaired recognition of objects *presented in unconventional orientations in MCI due to PD and AD was associated with decreased activation of frontoparietal regions, consistent with defective top-down regulation of visual processing.*

While some researchers have limited the use of the term dysexecutive syndrome to solely cognitive deficits, behavioural changes should also be included in the field of executive functions as long as they are due to impaired control. This top-down control operates both in the behavioural domain (inhibiting inappropriate behaviour) and in cognitive domain (focusing on the word's colour while inhibiting the urge to read the word in the Stroop interference task).

Table 1: Behavioral and cognitive dysexecutive disorders (Godefroy et al., 2018)

Behavioral disorders	Cognitive disorders
Assessed by direct examination of the subject's behavior or by administering an inventory	Assessed with tests
Highly suggestive impairments[a]	Highly suggestive impairments[a]
- Global hypoactivity with apathy and/or abulia - Global hyperactivity with distractibility and/or psychomotor instability and/or disinhibition - Stereotyped, perseverative behavior - Social behavior disorders (interpersonal skills, situation constraints, disinhibition, loss of empathy, and impulse control disorders)	- Action initiation and sustained alertness - Inhibition of prepotent/automatic action - Strategic lexical-semantic searching - Rules and concept generation and deduction - Planning - Set shifting

To facilitate research in the field of Executive Functions, authors (Diamond, 2013) have developed a tripartite classification that consists of:

- **Inhibition**, including inhibitory control, self-control (behavioural inhibition), and interference control (selective attention and cognitive inhibition). It includes the voluntary inhibition of dominant or automatic responses and would allow controlling behaviour, thoughts and emotions, as well as attentional aspects, with the aim to respond appropriately to the needs of the task and specific objectives,

- **Updating**, which allows keeping in mind and manipulating information. It involves the updating and the monitoring of the representations collected in the working memory (involvement of the Dorsolateral Prefrontal Cortex), which allow responding appropriately to external tasks or stimuli, thanks to the processing of relevant information,

- **Cognitive flexibility** (set-shifting), which allows modifying one's behavioural response to external stimuli. It is characterized by the attentional shift between tasks or between different mental operations. This mechanism is commonly regarded as disengagement from an irrelevant task with subsequent anchorage on a relevant task to pursue a particular objective.

Dysexecutive syndrome and Frontal lobe syndrome

Dysexecutive syndrome has to be distinguished from the frontal lobe syndrome, see Table 2. While dysexecutive disorders are only subcomponent of the frontal lobe syndrome, dysexecutive syndrome is defined in terms of impairment of control functions, regardless of the lesion site.

Table 2: Disorders of the frontal syndrome (Godefroy et al., 2018)

Functional domains	Disorders
Motor-gestural	- Paresis/paralysis - Frontal ataxia (gait apraxia) - Motor neglect - Gestural apraxia
Visuospatial and constructive abilities	- Oculo-motor disorders (including gaze grasping) - Visuo-spatial hemineglect - Constructional apraxia (especially observed for complex figures)
Language	- Speech articulation disorders (including apraxia of speech) - Broca's aphasia - Transcortical motor aphasia
Memory	Impairments of working memory: - the phonological loop (mild decrease in span and length effect) - the central executive (n-back, updating, delayed response tasks, and complex spans) Episodic memory: a range of profiles are observed: - impairment of strategic processes (the most specific profile) - storage impairment - selective impairment of target recognition
Executive Functions	Supramodal: observed regardless of input and output modalities[a] Behavioral disorders Cognitive disorders

[a] The distinction between executive function disorders and other deficits is based on the supramodal property and the absence of a lower-level impairment that can account for the deficit. For example, global hypoactivity is observed for all aspects of behavior (including motor and verbal output), in contrast to non-fluent aphasia, which selectively affects language output.

Anatomy of attention and executive functions processing and large-scale cognitive brain networks

All diseases affecting the frontal lobes and its interconnections with posterior lobes and subcortical structures may impact on executive functioning.

Large scale brain networks engaged in cognitive processes can now be easily visualized and studied e.g. by using resting state functional MRI and various analytical methods such as the seed-based functional connectivity analysis (a hypothesis-driven approach) or independent component analysis (ICA; a data-driven approach). Using these methods, several large-scale brain networks have been identified. **The fronto-parietal control network (FPCN) plays a central role in decision-making and cognitive task performance control.** It engages the anterior prefrontal cortex, insula, anterior cingulate, and anterior inferior parietal lobule, **see Figure 2**. The most anterior part of the prefrontal cortex has been suggested as the apex of the executive network underlying decision-making. Activations of insula and anterior cingulate cortex are commonly observed with a variety of cognitive control processes, particularly those involving conflict monitoring, information integration, and response selection. Finally, the anterior inferior parietal lobule region has been reported to increase activity during role transition in stimulus-response association tasks as well as tasks involving control of spatial attention. By being spatially positioned between the default mode network nodes and the dorsal attentional network nodes, the FPCN is thought to play a regulatory role in switching between them (Gao and Lin, 2012; Vincent et al., 2008). The **default mode network (DMN)** consists of the ventral medial prefrontal cortex, dorsal medial prefrontal cortex, posterior cingulate cortex, precuneus, and posterior inferior parietal lobules. Its activity and connectivity is suppressed during tasks, while it shows the highest connectivity at rest. Therefore, it is called the task-negative network. The DMN is involved in mind wandering, and is associated specially with internally directed cognitions. It has high connectivity with the hippocampus and according to some authors hippocampi make integral part of the DMN. On the other hand, the **dorsal attention network (DAN)** is particularly engaged in externally directed top-down visual attention control and it incorporates the dorsolateral prefrontal cortex, frontal eye field, middle temporal motion complex, inferior precentral sulcus, and superior parietal lobule. This network is particularly involved in working-memory tasks and in visual attention. The right fronto-parietal network also known as **ventral attention network (VAN)** includes the right prefrontal lateral regions (ventral frontal regions), insula and the right parieto-temporal junction. The VAN is engaged in sustained attention and orientation towards the behaviourally relevant stimuli, **see Figure 3**.

Figure 2: The frontoparietal control network (Gao and Lin, 2012)

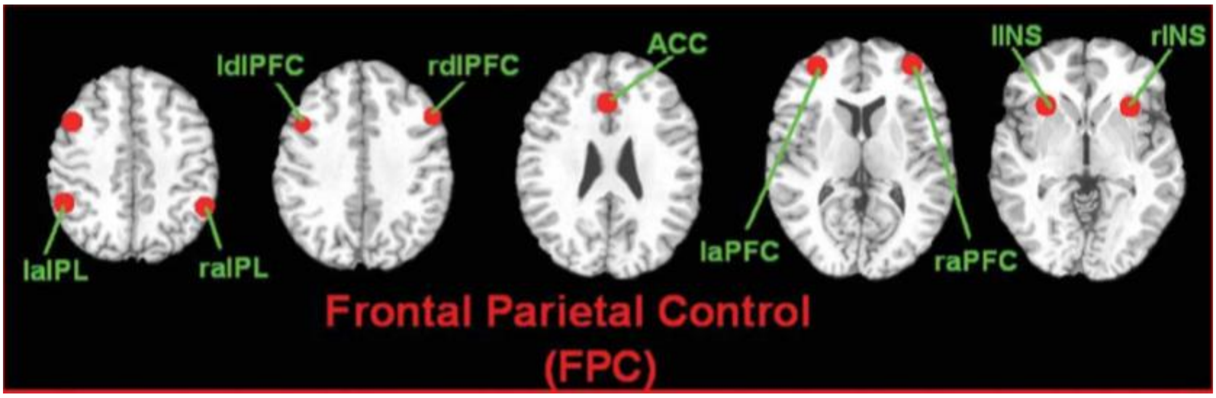
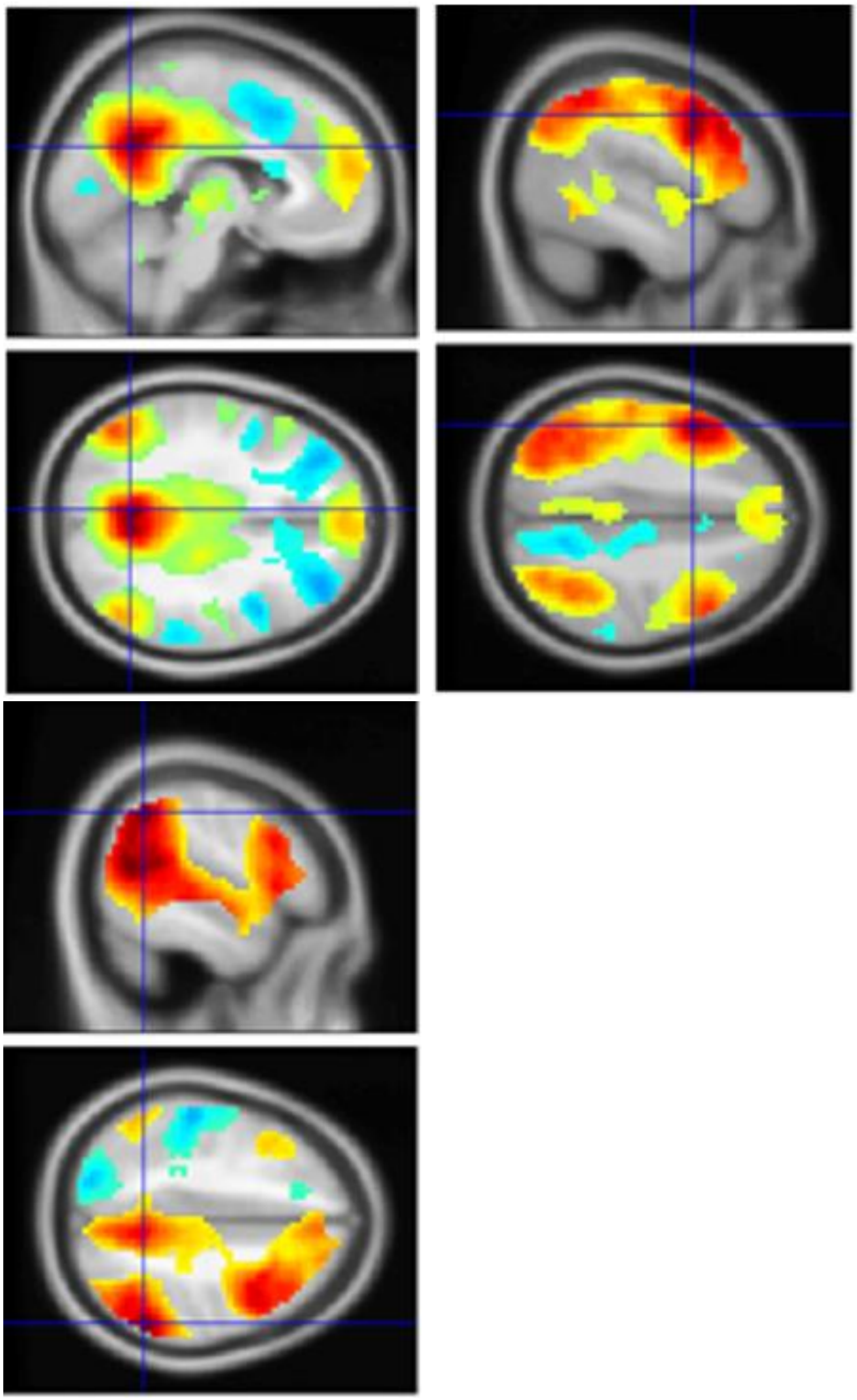
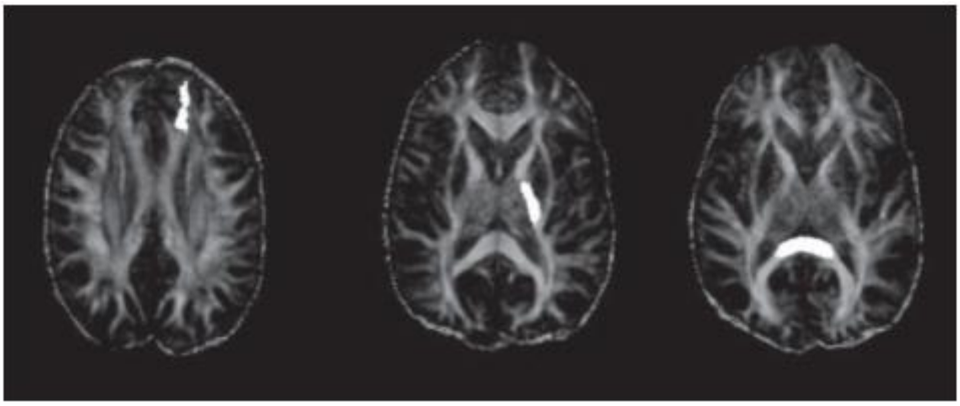


Figure 3: Large-scale brain networks as assessed by ICA (our own resting state fMRI data analysed in 50 healthy controls): default mode network (upper left), dorsal attention network (upper right), ventral attention network (lower left)



As for linking individual difference in **attention to white matter tracts**, the anterior corona radiata (ACR) ROI captures a segment of white matter that innervates left and right frontal and prefrontal regions implicated in functions of cognitive control (Posner, 2012). The splenium of the corpus callosum ROI contains white matter tracts that innervate and connect left and right parietal regions implicated in spatial orienting functions of attention. The posterior limb of the internal capsule contains white matter tract fibers that connect cortical regions to midbrain structures critical for alerting functions.

Figure 3: Single-subject fractional anisotropy maps (Posner, 2012): regions of interest demarcated in white, for the anterior corona radiata (left image), superior corona radiata (central image), and splenium of corpus callosum (right image)



Examination of attention and executive functions

Examples of tasks examining attention

Trail Making Test, part A (see examples of examining executive functions below)

Stroop task part 1 and 2 (see examples of examining executive functions below)

The Digit Symbols subtest from Wechsler Adult Intelligence Scale (WAIS) reflects visuomotor coordination, level of attention and concentration, motor speed, and the ability to learn a new task and maintain a steady response.

Digit Span forward and backward reflects working memory and level of attention and concentration.

While cognitive dysexecutive disorders are tested by using well-chosen tests in a cognitive battery, the behavioural dysexecutive disorders can be evaluated by direct examination of the behaviour or by behavioural inventory such as Neuropsychiatric Inventory (NPI).

Examples of tasks examining executive functions

The Trail Making Test (TMT), parts A and B. TMT A requires the subject to connect a sequence of numbers dispersed across a page as quickly as possible without lifting the pen from the paper, and is a simple measure of behavioural regulation and motor speed. In TMT B, the subject alternates between sequences of numbers and letters, which necessitates alternating the mental sets (switching attention between two types of items). For each version, the time to complete the task is recorded.

The **Verbal fluency tasks** are used as a measure of semantic and verbal production as well as of working memory and executive function. Both Phonological Fluency (in Czech the letter cues are: N, K, and P), and Verbal Semantic Fluency (category: e.g. animals) are tested. The mean number of words per minute is the outcome measure.

The **Stroop task** requires the subject to name the colour of the ink in which a coloured word is printed. While the first part (reading of words printed in the black inn) and the second part (naming colours of crosses) examine attention, the third (interference) section consists of words (names of colors), ink colors differing from the written word (incongruent ink color). Thus the third part of the Troop test specifically concerns proactive interference and the ability to ignore habitual responses. The calculated Stroop interference T-score is usually an outcome measure.

In the **Tower of London** task evaluates particularly the spatial planning and task execution. In this task, disks have to be moved from a starting configuration on three sticks of equal length to a target arrangement. The target array is presented as a coloured drawing and the subject's task is to solve the problem with the minimum number of possible moves. Usually several levels of cognitive difficulty are tested.

The Wisconsin Card Sorting Test (WCST) is aimed to evaluate abstract reasoning, and cognitive flexibility understood as the ability to change one's strategies in response to environmental contingencies. The WCST consists of four stimulus cards and two sets of 64 response cards. The cards vary in colour, shape and number of elements represented. The test includes some ambiguous stimuli, and the pairing criteria vary according to a standardized order (Colour, Form, Number). The task requires identifying the correct criterion with which to order the response cards to the stimulus cards; for each card placed by the participant, the experimenter provides feedback on the correctness of the performance. Based on the feedback from the experimenter, the participant can modify his/her behaviour by identifying the appropriate strategy.

The Flanker Task measures selective attention and the ability to control conflictual information. The task requires discriminating the central target stimulus between a series of lateral distractors (flanker). There are three types of conditions: the congruent trials, in which the target stimulus and the flankers have the same characteristics and required the same response; the incongruent trials, in which the target has different features with respect to the distractors, requiring an opposite response that generates conflict; finally, the neutral condition, in which the distractor is not confused with the targets presented in the task, and it does not cause conflict. The flanker effect (also called conflict or congruence effect) reveals the difficulty in ignoring the distractors due to the ambiguity of the stimuli used.

The Go/No-Go Task assesses sustained attention (vigilance) and impulsivity and allows obtaining information related to motor-type inhibitory control. The task consists in the presentation of a stimulus that requires a response from the participant (Go stimulus), and another stimulus for which the participant must, instead, inhibit any response (No-Go stimulus). A high percentage of errors indicates a difficulty in behavioural inhibition.

Dysexecutive disorders in neurological diseases

T**able 3: Main brain diseases in which executive function is altered** (Godefroy et al., 2018)

Stroke/vascular cognitive impairment	Supratentorial infarct and hemorrhage
	Complicated ruptured aneurysm (especially of the ACoA)
	Cerebral venous thrombosis (especially of the superior sagittal sinus)
	Anoxia/hypoxic encephalopathy
	Extensive white matter abnormalities (action slowing)
Other focal lesions	Tumors (including third ventricle cysts)
Degenerative diseases	Fronto-temporal lobar degeneration; Amyotrophic lateral sclerosis
	Fronto-subcortical dementia (PSP, HD, PD, Wilson's disease)
	Alzheimer's disease
	Lewy body disease
	Fragile X-Associated Tremor/ataxia syndrome
Severe traumatic brain injury	
Inflammatory/infectious diseases	Multiple sclerosis
	Encephalitis (HIV, HSV), Creutzfeldt Jakob diseases
Others	Encephalopathy with alcohol abuse-vitamin deficiency
	Hydrocephalus

PSP, progressive supranuclear palsy; HD, Huntington's disease; PD, Parkinson's disease; HIV, Human immunodeficiency virus; HSV, herpes simplex virus; ACoA, anterior communicating artery.

Examples of dysexecutive syndrome in the most common neurodegenerative brain diseases

Dysexecutive disorders are present in most brain diseases and they are closely related to difficulties in performing instrumental activities of daily living. About 90% of **Alzheimer's disease (AD)** patients present with executive functions disorders at the initial assessment. The AD profile is characterized by apathy as behavioural component and impaired planning, flexibility and inhibition as cognitive component (Godefroy et al., 2018). According to recent studies (Whitwell et al., 2012) the hippocampal sparing variant of AD displayed more severe deficits in executive functions as compared to typical AD or limbic variant AD although memory impairment could also be present in this AD subtype. Ratio between the hippocampal and cortex volumes as assessed by MRI predicted the pathologically confirmed variants of AD; with the lowest ratio being in the limbic dominant subtype and the highest ratio in the hippocampus sparing subtype. Interestingly, this ratio also predicted the slope of cognitive decline such that patients with higher hippocampus/ cortex ratio (i.e. hippocampus sparing variant of AD) had faster cognitive decline (Risacher et al., 2017).

Neuropsychological studies have provided evidence that executive function is usually affected in nondemented patients with **Parkinson's disease**. It has been documented that measurable mild cognitive impairment (MCI) is present in approximately one-fourth to one-third of people newly diagnosed with PD (Litvan et al., 2012). This impairment has been related to the dysfunction of the dorsolateral striatoprefrontal loop consecutive to the loss of dopaminergic nigral neurons, as well as the mesocortical pathway in which neurons project predominantly from the ventral tegmental area and medial substrantia nigra pars compacta to the neocortex. Functional neuroimaging studies also provided evidence for a role of both disruption in the nigrostriatal and mesocortical pathways. In addition to deficits of dopamine, the cholinergic system has also been implicated in cognitive dysfunction and in PD dementia in particular, and serotoninergic or noradrenergic systems could also be involved.

In MCI-PD, attention/executive function deficits seem to be most prevalent. MCI-PD increases the risk of PDD; however, the posterior cortical dysfunction with impaired semantic language, praxis (figure drawing/copying), and visuospatial deficits is associated with fast conversion into PD-dementia (Williams-Gray et al., 2009). *For more details on cognitive impairment and dementia in PD*

as well as behavioural disorders including apathy and impulse controls disorders in PD, see the review article in pdf (Rektorova, 2019, open access).

Behavioural variant of frontotemporal dementia (FTD) as a "model" dysexecutive disorder

Executive dysfunctions are highly prominent in this variant of FTD (Rascovsky et al., 2011). Five behavioural disorders are major criteria: global hypoactivity with apathy, loss of empathy, disinhibition (prominent in social behaviour), stereotyped behaviour, and hyperorality.

Suggested literature

Diamond A. Executive functions. Annu Rev Psychol. 2013;64:135-68. doi: 10.1146/annurev-psych-113011-143750. Epub 2012 Sep 27. Review.

Gao W, Lin W. Frontal parietal control network regulates the anti-correlated default and dorsal attention networks. Hum Brain Mapp. 2012 Jan;33(1):192-202. doi: 10.1002/hbm.21204.

Godefroy O, Martinaud O, Narme P, et al.; GREFEX study group. Dysexecutive disorders and their diagnosis: A position paper. Cortex. 2018 Dec;109:322-335. doi: 10.1016/j.cortex.2018.

Litvan I, Goldman JG, Tröster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord. 2012 Mar;27(3):349-56. doi: 10.1002/mds.24893.

Nemcova Elfmarkova N, Gajdos M, Rektorova I, et al. Neural evidence for defective top-down control of visual processing in Parkinson's and Alzheimer's disease. Neuropsychologia. 2017 Nov;106:236-244. doi: 10.1016/j.neuropsychologia.2017.09.034

Posner MI, ed. Cognitive Neuroscience of Attention. THE GUILFORD PRESS New York, 2012, 2nd ed.

Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011 Sep;134(Pt 9):2456-77. doi: 10.1093/brain/awr179.

Rektorova I. Current treatment of behavioral and cognitive symptoms of Parkinson's disease. Parkinsonism Relat Disord. 2019 Feb 28. pii: S1353-8020(19)30087-2. doi: 10.1016/j.parkreldis.2019.02.042.

Risacher SL, Anderson WH, Charil A, et al.; Alzheimer's Disease Neuroimaging Initiative. Alzheimer disease brain atrophy subtypes are associated with cognition and rate of decline. Neurology. 2017 Nov 21;89(21):2176-2186. doi: 10.1212/WNL.0000000000004670.

Vincent JL, Kahn I, Snyder AZ, et al. Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. J Neurophysiol. 2008 Dec;100(6):3328-42. doi: 10.1152/jn.90355.2008

Whitwell JL, Dickson DW, Murray ME, et al. Neuroimaging correlates of pathologically defined subtypes of Alzheimer's disease: a case-control study. Lancet Neurol. 2012 Oct;11(10):868-77. doi: 10.1016/S1474-4422(12)70200-4.

Williams-Gray CH, Evans JR, Goris A, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. Brain. 2009 Nov;132(Pt 11):2958-69. doi: 10.1093/brain/awp245.