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Review

The neuropsychological profile of early and continuously treated phenylketonuria: orienting, vigilance, and maintenance versus manipulation-functions of working memory

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Abstract

In this paper, we review neuropsychological test results of early and continuously treated Phenylketonuria (PKU) patients. To increase insight into the neuropsychological profile of this population, we have attempted to place the results within an attentional network model [Images of the mind, 1994], which proposes interacting but dissociable attentional networks for orienting, vigilance, and executive control of attention. Executive control of attention is discussed against the background of the process-specific theory of working memory (WM) [Handbook of neuropsychology, 1994], which postulates a distinction between the 'maintenance'-function of WM and the 'manipulation and monitoring'-function.

Neuropsychological results are presented for 67 early and continuously treated PKU patients and 73 controls aged 7–14 years. Four neuropsychological tasks were employed to measure orienting, mnemonic processing, interference suppression, and top-down control in visual search. No differences were found in orienting and the maintenance-function of WM. In addition to previously reported impairments in sustained attention/vigilance and inhibition of prepotent responding, PKU patients exhibited deficits when top-down control was required in a visual search task, but showed no impairment when interference suppression was required. It is discussed how the specific neuropsychological impairments in PKU may be a consequence of mid-dorsolateral prefrontal cortex (DLPFC) dysfunctioning due to deficiencies in catecholamine modulation.

Keywords: Phenylketonuria; Phenylalanine; Tyrosine; Selective attention; Vigilance; Sustained attention; Working memory; Prefrontal cortex; Dopamine; Noradrenaline

Contents

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1. Introduction

Phenylketonuria (PKU) is caused by mutations in the gene that codes for the liver-based enzyme phenylalanine hydroxylase, the enzyme responsible for the conversion of the amino acid phenylalanine (Phe) into the amino acid tyrosine (Tyr) [101]. Deficient conversion leads to accumulation of Phe and low to normal concentrations of Tyr in blood and tissues. Neuropsychological impairments in treated PKU have been associated with high blood Phe levels [32,44,93,100,108,110,116,118]. High blood Phe levels can have a deteriorating influence on (the speed of) information processing, while high brain Phe levels interfere with myelination of neuronal axons [8]. High blood Phe levels can also cause specific cognitive deficits related to neurotransmitter deficiencies, when they interfere with normal transport ratios of neurotransmitter precursors at the blood–brain barrier. Phe and the other large neutral amino acids (LNAAs), including Tyr, the metabolic precursor of dopamine and noradrenaline, and tryptophan, the metabolic precursor of serotonin, use the same transport proteins to cross the blood–brain barrier. High blood Phe levels can result in carrier saturation and competitive inhibition of other LNAAs [84,104]. In this study we attempt to specify which aspects of attention and information processing are deficient and which are not in early and continuously treated PKU.

We will conceptualise the neuropsychological profile of PKU patients in terms of the attentional network model proposed by Posner and Raichle [91]. In this model three interacting anatomical networks are distinguished, carrying out the functions of orienting to sensory stimuli (selective attention in visual search), achieving and maintaining an alert state (vigilance and sustained attention), and orchestrating voluntary actions (executive control) [36,91].

In the orienting network three forms of orientation can be distinguished. Overt orienting involves directing the eyes or head toward the location of interest. Covert orienting involves assigning priority to an area of the visual field by exogenous or endogenous cueing without relying upon head or eye movements, and visual search involves scanning a number of stimuli for a target with specific properties by which it can be distinguished from the other presented stimuli. When, during covert orienting, a cue attracts attention to a location distinct from where the target is presented, a disengagement from the cued location, an attentional movement, and an engagement at the target location are required. In a visual search task similar cognitive operations are required. Attention must be disengaged, moved, and engaged at a new location until the target has been detected [36,91]. Anatomically, overt and covert orienting and visual search activate the precentral gyrus of the frontal lobe and areas in the parietal lobe [17,87,91]. It should be emphasised that the selective allocation of attention to a particular part of the visual field, for example in visual search tasks [35], is regarded as one of the components of selective attention in the traditional definition of selective attention [86]. Another important component involves inhibition of attention to distracters, i.e. 'filtering' of certain attributes of an object for processing whilst excluding other attributes and objects [86]. This aspect of selective attention belongs to the executive control network in the Posner and Raichle model [91].

Vigilance is the ability to achieve and sustain an alert state. Tasks using a warning signal have been employed to examine how quickly a person can reach maximum alertness. Continuous performance tasks have been employed to study vigilance and sustained attention. These tasks usually require participants to remain prepared to detect relatively rare and generally rather weak targets. Right frontal and parietal areas and the locus coeruleus are of particular importance for vigilance and sustained attention [16,18,53,75,90,91,119,120].

Executive control of attention has been related to goal directed behaviour, error detection, conflict resolution, inhibition of automatic responses, handling novelty, task-switching, and emotional self-regulation [7,36,91]. Typical lists of executive functions additionally include set-maintenance, integration across space and time, and working memory (WM) [77]. The majority of neuropsychological tasks require more than one of the aforementioned cognitive operations. Brain networks associated with executive control include the anterior cingulate cortex (ACC) and supplementary motor area (SMA), the orbitofrontal cortex, the dorsolateral prefrontal cortex (DLPFC), ventrolateral PFC, portions of the basal ganglia and the thalamus [36,82,91].

2. Interactions between attentional networks

The networks of attention interact and depend, in part, on the same brain structures, but can be dissociated. For example, in a previous study with PKU patients and healthy controls we used a continuous performance task to assess vigilance, sustained attention, and executive control [44]. Executive control was assessed by examining inhibition of biased response tendencies. Bias was induced by requiring twice as many responses with the non-preferred hand compared with the preferred hand. Bias increased with time on task, particularly for PKU patients. This interaction indicates that inhibitory control was influenced by the ability to sustain attention. A similar finding was reported for ADHD children [24,103].

The attentional network for vigilance and sustained attention has been located in a right frontal–parietal system even when no stimulus occurred [75]. The vigilance network appears to be located in the right hemisphere independent of whether the visual, auditory or somatosensory modality is concerned [16,75]. Coull et al. [19] compared regional cerebral blood flow (rCBF) during a simple visual sustained attention task with rCBF during

the rapid visual information processing task (RVIP). RVIP requires sustained attention, selective attention to the beginning of predefined target sequences, and WM to hold the selected stimulus on-line and compare it to the subsequent stimulus for rejection or inclusion in the target sequence. Upon subtraction of rCBF during the simple sustained attention task from rCBF during RVIP, right-sided frontal activations (superior and inferior frontal gyrus) were no longer apparent, indicating that these activations are associated specifically with sustaining attention.

Orienting and vigilance also interact. A cue in a covert orienting task facilitates orienting and changes the level of alertness [36]. The parietal lobe is part of both the attentional networks for orienting and vigilance/sustained attention. Noradrenaline (NE) strongly innervates the parietal lobe [69] and is associated particularly with vigilance [88,94]. Evidence has been provided that methylphenidate, a stimulant drug that acts to increase the synaptic concentration of dopamine (DA) and NE by blocking their reuptake [102], and consequently affecting vigilance, enhances orienting [24]. To investigate whether the mechanisms of orienting and alerting are dissociable, Fernandez-Duque and Posner [35] conducted orienting experiments in which the level of alertness was manipulated. Mean reaction time (RT) of valid trials, in which a cue correctly predicted the future location of a target, was subtracted from mean RT of invalid trials (in which the target occurred in any of the uncued locations), to obtain the level of orienting. It was then examined whether increasing the level of alertness, resulting from adding an auditory cue to a visual cue, produced more rapid orienting. The level of orienting was not found to be influenced by alertness.

The orienting and executive control networks have also been shown to interact. In a study investigating the relationship between visuospatial search and object WM, Pollmann and Von Cramon [87] showed overlapping activity, in frontal eye-field (FEF), preSMA/SMA, precentral gyri, and branches of the intraparietal sulcus (IPS), for object WM and visuospatial search. However, the right DLPFC was only significantly involved when difficulty of the object recognition process increased and more attention was demanded, suggesting a role of right DLPFC in top-down control of orienting.

3. Working memory: maintenance versus manipulation and monitoring

While attempting to understand the nature of information processing deficits in PKU insight into what is meant by executive control is needed [34]. WM is considered central to executive control [6,13]. Posner and Raichle [91] defined WM as the representation of information in its absence and the control of activation of these representations. WM has also been defined as the active maintenance and manipulation of information for brief periods to guide future motor and cognitive processes [6]. The process-specific model of WM proposes a distinction between the 'maintenance'-function and the 'manipulation and monitoring'-function of WM [78,80]. The maintenance-function of WM is concerned with holding information on-line and mnemonic processes such as active selection, comparison, and judgement of stimuli held in short-term and long-term memory. In contrast, the manipulation and monitoring-function is involved in 'strategic' or higher level executive processes [78,80]. More specifically, this WM-function involves recoding maintained information for the purpose of planned action [81]. The recoding of information, in turn, is required when new stimulus–response (S–R) associations (attentional sets) have to be adopted or when tasks demand switching between or continuous monitoring of diverse S–R associations [81,96]. These cognitive operations usually demand inhibition of prepotent responding. An example of when recoding maintained information involves inhibition of prepotent responding was provided in a study by Casey and colleagues [15]. In a flanker task, subjects were biased by the presentation of a series of compatible trials. Inhibitory control had to be exerted over the 'automated' S–R association when an incompatible trial followed a series of compatible trials.

Inhibiting the selection of prior choices is also considered a manipulation-function: subjects have to continually update an on-line record of which particular stimuli (whether they are locations, concrete stimuli, or abstract designs) have been previously selected [74,81]. Since subjects are not biased, they do not have to overrule a prepotent response tendency. Instead, subjects have to demonstrate the ability to suppress interference.

Manipulation of WM-content without inhibitory demands is also possible. Pollmann and Von Cramon [87], for example, employed a task in which subjects were required to search a display consisting of 11 'paperclip'-stimuli for a target paperclip and respond by pressing a 'present' or an 'absent' button. The difficulty of object matching was varied by changing the viewpoint of cue and target objects. Manipulation of WM-content was operationalised as requiring a 'top-down' controlled search for the target, as opposed to a 'pop-out' effect of the target within the distracter array. Finally, the demand for monitoring or manipulation of WM-content may result from supraspan WM loads. When load exceeds a certain maximum, a simple maintenance task may require continuous monitoring and updation of the contents of WM [99].

4. Neural correlates of WM: maintenance versus manipulation and monitoring

Goldman-Rakic and colleagues [40,41,52] have proposed a modality-specific architecture of prefrontal cortical areas for WM. In this model visuospatial processing is mediated by the dorsolateral PFC, object processing

engages the ventrolateral PFC/inferior convexity, and verbal WM and subvocal rehearsal crucially involve Broca's area (BA 45/47) and other areas related to semantic processing. Although Goldman-Rakic and colleagues suggested that storage and processing functions are integrally related in each area, the modular architecture is specifically supported for basic mnemonic processing, i.e. the maintenance-function of WM [21,22,61,62,72,105,114]. For example, McCarthy et al. [62] examined maintenance-functions of WM with spatial, object, and simple perceptual target detection tasks. The spatial and object tasks activated the middle frontal gyrus more than the simple detection task (in which the target was a dot). The spatial task activated the right middle frontal gyrus, whereas the object task resulted in bilateral frontal gyrus activity. The object task also activated the left inferior temporal gyrus. For verbal maintenance-functions, examined with item recognition and 0-, or 1-back tasks, activations have been reported in left posterior parietal cortex, Broca's area, left supplementary motor and premotor areas [2,37,47,106].

With regards to manipulation and monitoring-functions of WM no anatomical segregation for object and spatial modalities has been found [23,27,73,74]. Curtis et al. [23] reported increased blood flow in dorsolateral, but not ventrolateral PFC during a non-spatial object WM task requiring a high level of monitoring. In a study comparing a spatial WM task with a spatial control task, and a non-spatial WM task with a non-spatial control task, almost identical bilateral increases in mid-DLPFC were demonstrated for the WM tasks compared to the control tasks [73]. It has, however, been recognised that other areas considered to be part of DLPFC provide domain-specific input to mid-dorsolateral PFC (dorsal BA 46 and 9/46 and area 9). Visuospatial input is received from the posterior dorsolateral region (BA 8 and 6) and from the cortex within the middle part (sulcal BA 46) and the caudal part (BA 8) of the sulcus principalis. Non-spatial visual (object) input originates from the ventrolateral PFC [83].

There is evidence for anatomically separable maintenance and manipulation and monitoring-functions of WM [10,71,74,79,80]. Owen et al. [74] reported a significant change in blood flow in the right mid-ventrolateral frontal cortex, but not in the mid-dorsolateral frontal cortex, during maintenance of a 'spatial span' in WM. During a '2-back' task that required subjects to continually update and manipulate an ongoing sequence of locations within WM, blood flow increases were observed in both frontal regions, but a direct comparison between the two tasks revealed that only the manipulation task resulted in significantly greater activity in the right mid-dorsolateral frontal cortex. Petrides et al. [82] recently provided evidence for a regulatory role of the orbitofrontal cortex during the processing of stimuli that deviate from expectations, and therefore need to be evaluated. This study further indicated involvement of the mid-ventrolateral PFC in explicit decisions on the contents of memory and of the mid-dorsolateral PFC during monitoring. In the control condition, subjects viewed a pair of images on a computer screen and then touched the screen in the space between the two stimuli to advance to the next pair. In the 'deviation'-condition noticeable distortions, such as a thick black line, were introduced in the images. In the 'explicit decision'-condition, subjects were required to touch the stimulus that had not been present in previous presentations, and in the 'monitoring'-condition, subjects had to keep track of their earlier choices, and select the stimulus that had not been selected in previous trials.

Another brain region that has been shown to be involved in 'manipulation' of WM-content is the ACC [5,10,14,15,36,59,89]. MacDonald et al. [59] reported a double dissociation in a Stroop paradigm between (left) DLPFC, which was selectively engaged during the preparatory period, more for colour naming (requiring greater control) than for word reading (a more automatic response), and ACC, which was selectively activated during the response period, more for incongruent than for congruent colour naming trials. This result suggests a role of DLPFC in representing and actively maintaining the attentional demands of the task and a role for ACC in conflict monitoring and response selection.

5. Dissociating interference control and response inhibition

It should be noted that neither the attentional network model nor the process-specific model distinguish between selective attention involving inhibition of irrelevant distracters (interference suppression) and inhibition of prepotent responding (response inhibition). In the attentional network model, both would be classified as executive control, whereas in the process-specific model, both would be classified as manipulation and monitoring-functions of WM. There is increasing evidence, however, that response inhibition and interference suppression should be distinguished [9,18]. Bunge et al. [9] showed that these different types of cognitive control have different developmental time courses. Age-related differences in interference suppression were particularly associated with differences in VLPFC-engagement, whereas differences in response inhibition were associated with differences, between children and adults, in DLPFC-involvement. Corbetta and Shulman [18] reviewed the evidence for the recruitment of dorsal fronto-parietal regions during top-down cognitive selection of stimuli and actions, and of (right-lateralised) tempero-parietal and ventral regions during the detection of behaviourally relevant sensory events. The authors emphasised the interactions between the two systems. When information that must be selected for responding has clear pop-out features and remains unchanged, subjects can readily filter out irrelevant stimulus information. However, when stimuli are novel or unexpected and bottom-up processing no longer suffices, the ventral fronto-parietal

network may work as an 'alerting system' or 'circuit breaker' for the dorsal system, interrupting ongoing cognitive activity and directing attention to salient events [18]. Thus, Corbetta and Shulman propose an extension of the function of ventrolateral regions beyond mnemonic processing, particularly when their interactions with dorsal systems are concerned. The authors recognise that neurons in dorsal areas are also activated during filtering (and consequently during interference suppression), but argue that these neurons mainly respond to the relationship between target and distracter stimuli (larger responses when there is greater similarity between target and distracter or when distracters have served as targets in previous sessions). Corbetta and Shulman postulate that the orienting function in Posner's attention network model (posterior attention system), may be part of the dorsal fronto-parietal system of goal-directed attention [18].

We now proceed with a conceptual review of neuropsychological findings in PKU to find out whether they can be placed within the framework of attention and WM presented earlier.

6. PKU and specificity of neuropsychological deficits

We have performed a number of studies with a population of 7–14 year old early and continuously treated PKU patients and age-matched controls [44–46]. In order to examine motor control, stability and accuracy have been compared for highly automated circular movements and 'new', unpredictable movements. For PKU patients, an increase of deficits in motor control was found when unpredictable movements were required compared to when the task could be performed according to one predefined, unchanging S–R association. History of dietary control predicted performance: higher Phe levels were associated with less accurate and unstabile movements [46].

In order to examine inhibition of prepotent responding and attentional flexibility, a task consisting of three parts was used. In Part 2 of the task, subjects had to acquire a new S–R association which was opposite to the S–R association (attentional set) demanded in task Part 1. Consequently, the S–R association of task Part 1 (which was also the more 'natural' response tendency, i.e. follow the direction of a moving stimulus) had to be inhibited. In Part 3 of the task, subjects were required to alternately and unpredictably apply one of the two acquired S–R associations, dependent on stimulus characteristics. PKU patients exhibited deficient inhibition of prepotent responding and attentional flexibility [45]. Inhibition of prepotent responding was predicted by historical Phe levels, whereas attentional flexibility was predicted by both historical and concurrent Phe levels. Similar findings were observed for vigilance, sustained attention, and inhibition of biased response tendencies [44]. These studies indicate deficient vigilance/sustained attention and impairments in manipulation and monitoring of WM-content in PKU.

Other studies examining children and (young) adolescents with PKU have demonstrated deficits that can also be attributed to a dysfunction of the vigilance and executive control networks. Vigilance deficits during a continuous performance task have been consistently reported [11,25,100,116]. A wide variety of executive control impairments have been reported by Welsh et al. [118]. These authors found poorer performance of PKU patients compared with controls on a visual search task, a verbal fluency task, a motor planning task, and the Tower of Hanoi task. In the visual search task, eight occurrences of a target among 32 distracters had to be detected. Manipulation of WM-content is required because targets in one trial were distracters in another trial, thus demanding inhibition of previously relevant S–R associations. The verbal fluency task required subjects to generate as many different members of a semantic category as possible within 40 s. Switches between the four employed categories required subjects to suppress naming members of a previous category or make repetitions and modifications. This demands inhibition of the previously relevant attentional sets and continuous monitoring of WM-content. The motor planning task involved finger sequencing, i.e. touching each of the four fingers to their thumb in order to start with the ring finger. This movement pattern cannot be performed automatically and requires continuous monitoring. The Tower of Hanoi disk-transfer task requires more than just holding the goal configuration in WM. The steps towards this goal configuration have to be planned as efficiently as possible, without violating the rules of the task. This involves continuous monitoring of and switching between these rules.

Diamond and colleagues [28,32] showed that PKU children with relatively high concurrent Phe levels had difficulties with holding information in WM while, at the same time, they had to inhibit prepotent responding. For example, subjects had to say 'day' when shown a black card with the moon and stars on it, and 'night' to a white card containing a sun. This task requires holding two rules in WM and inhibition of a strong, 'prepotent' S–R association. Weglage et al. [116] found deficient performance of early treated PKU patients with (relatively) high concurrent Phe levels on the colour-word-interference-task (CWIT). The task part in which the colour of the words has to be named requires subjects to inhibit a strong, prepotent S–R association, i.e. to read the words.

There is also evidence suggesting that early treated PKU patients are not impaired with regards to maintenance-functions of WM [32,116,118]. Diamond et al. [32] did not find impaired performance by PKU patients on the Corsi–Milner block tapping test, a task measuring spatial span (temporal order memory). Welsh et al. [118] found no deficits on a picture recognition task, and Weglage et al. [116] did not find differences between PKU patients and

controls in performance of a digit-span task. Both tasks required only mnemonic processing.

Several authors, however, found no differences between controls and PKU patients on tasks requiring executive control or WM-monitoring/manipulation. Diamond et al. [32] did not observe deficits for PKU patients on a self-ordered pointing task, in which subjects had to continually update an on-line record of which particular stimuli were selected previously. Stemerdink et al. [109] found no differences between controls and PKU patients on the Eriksen flanker task. Note, however, that these tasks require interference suppression, whereas the tasks showing deficits in PKU usually required response inhibition.

In order the further complete the neuropsychological profile of treated PKU patients, the goals of the present study were (a) to investigate selective attention in visual search (orienting), (b) to investigate interference suppression (filtering), (c) to examine WM-maintenance, and (d) to find out whether a manipulation-deficit in PKU extends beyond inhibition of prepotent responding. For this purpose, a task measuring top-down controlled visual search, was selected.

7. Method

For the present study, a nation wide Dutch population of 67 early and continuously treated PKU patients between 7 and 14 years old and 73 age-matched controls performed nine neuropsychological tests from the Amsterdam neuropsychological tasks (ANT) [26]. In accordance with present treatment guidelines for children and young adolescents with PKU [70], patients were allocated, for statistical analysis, to a PKUlo group when concurrent Phe levels were $\leq$360 μmol/l, or a PKUhi group, when concurrent Phe levels were higher than 360 μmol/l. In addition, subjects were allocated to a young group (age $<$ 11 years) and an older group (age $\geq$ 11 years) to investigate whether possible differences between controls and PKU patients decreased during early adolescence. Subject characteristics of the total population are presented in Table 1. Two patients were excluded from the original sample because they should have been diagnosed as non-PKU hyperphenylalaninemia. Two controls and two patients were excluded because they followed special education for children with learning difficulties or behavioural problems. Furthermore, one control and two PKU patients had WISC-R IQ-scores below 75. Finally, for every task, subjects were excluded from statistical analysis when they were unable to perform or complete the task, or demonstrated a high number of statistical outlier scores. This resulted in 68 patients and 57 controls for analysis of the memory search task, 65 controls and 55 patients for the focussed attention task, 69 controls and 56 patients for the flanker interference task, and 67 controls and 58 patients for the feature identification task. The study was approved by the ethical committees of the treatment centres where patients received regular follow-up care, and the Dutch National PKU Steering Committee. Written informed consent was obtained from parents or caretakers of the participants before the start of the study.

Table 1
Subject characteristics

	N	Male	Female	Age (SD)	Conc. Phe (SD)	IDC (SD)
Controls						
Young	39	22	17	9.19 (1.31)		
Old	34	22	12	12.89 (1.22)		
Total	73	44	29	10.91 (2.25)		
PKUlo						
Young	16	11	5	8.98 (1.69)	221.3 (78.1)	287.4 (64.1)
Old	13	5	8	13.0 (1.19)	209.0 (115.2)	307.1 (70.0)
Total	29	16	13	10.78 (2.5)	215.8 (94.8)	297.7 (66.3)
PKUhi						
Young	17	6	11	8.93 (0.87)	568.8 (156.8)	355.6 (93.5)
Old	21	8	13	12.59 (1.08)	673.0 (218.6)	366.7 (99.4)
Total	38	14	24	10.95 (2.09)	626.4 (198.0)	362.2 (95.7)

Young, age $<$ 11 years; old, age $\geq$ 11 years. PKUlo, concurrent Phe $\leq$ 360 μmol/l; PKUhi, concurrent Phe $>$ 360 μmol/l. IDC, Index of dietary control (mean of all half-year median Phe levels).

The results of four out of the nine ANT-tasks, measuring vigilance/sustained attention, inhibition of prepotent responding and set-shifting, and motor control were described earlier in this paper. A (fifth) task, with very low cognitive demands, confirmed a generally prolonged speed of information processing in PKU patients [44]. The results of four tasks, measuring selective attention in visual search (orienting: memory search task), maintenance of information in WM (memory search task and focussed attention task), filtering (focussed attention task and flanker interference task), and controlled visual search (manipulation of WM-content: feature identification task) will be presented later. All statistical analyses were conducted with group (controls, PKUlo, and PKUhi) and age (age $\leq$ 11 years and age $>$ 11 years) as independent variables. For every task, RT and error percentage were the dependent variables. Simple contrast analyses were performed to examine group differences in more detail.

8. Results

8.1. Memory search

In the memory search task, subjects searched consecutive signals, consisting of four consonants for one (Part 1 of the task), two (Part 2 of the task), or three target letters (Part 3 of the task). A 'yes'-response (mouse button press) was required when all letters of the memorised set were present (50% of the signals) (Fig. 1).

RT and accuracy when the load was 1, demanding only disengaging, moving, and engaging attention until the target or the absence of a target was detected, represented

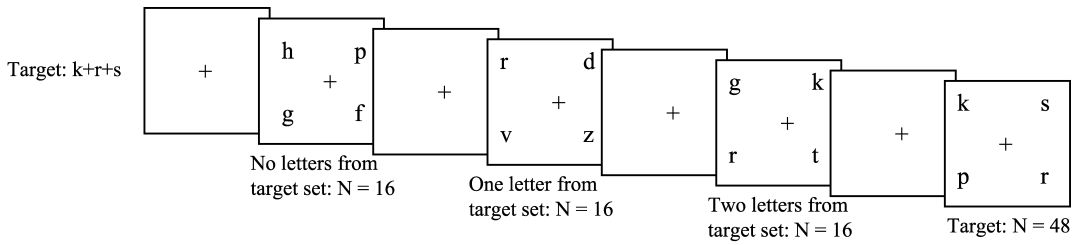

Fig. 1. Memory search: design.

efficiency of selective attention in visual search/orienting. Loads of two and three target letters were excluded since maintaining more than one target in WM could slow down or hamper performance. A one-way ANOVA showed no significant difference in mean RT between controls, PKUlo, and PKUhi patients $[F(2,126) = 1.5, p > 0.2]$. One-way ANOVA did not result in significant group differences with respect to accuracy either $[F(2,126) = 1.7, p > 0.1]$.

Repeated measures analyses with load (1 versus 2 versus 3 target letters) as within-subjects factor were performed to establish whether a differential change in mean RT and error percentage was present for controls, PKUlo, and PKUhi patients when the number of target letters that had to be maintained in WM increased. Prolonged RTs were observed when more letters constituted the target set $[F(1,242) = 358.4, p < 0.001]$. There was no significant interaction of load with group, indicating that PKU patients did not experience more difficulties than controls when more target letters had to be maintained in WM. There was no significant main effect for group.

A similar repeated measures procedure was performed for error percentage in task parts one to three. Mean error percentage increased significantly when load increased $[F(2,242) = 4.6, p < 0.05]$, but there was no significant interaction between load and group.

A significant effect of group $[F(2,121) = 5.6, p < 0.01)$ indicated greater inaccuracy in PKUhi patients compared with controls (Contrast estimate (CE) $= -1.825$, $p < 0.01$), and compared with PKUlo patients (CE $= -1.459$, $p < 0.05$). PKUlo patients and controls did not differ significantly.

8.2. Focussed attention

In this task, subjects were required to search a display consisting of four consonants, for one (Part 1 of the task) or one of three target letters (Part 2 of the task) on two relevant locations (upper left and lower right). The other two locations had to be ignored. The relevant locations remained unchanged throughout the task. Thus, this task measured filtering by requiring inhibition of yes-responses to targets on irrelevant locations (Fig. 2). In addition, different loads in task parts 1 and 2 enabled us to examine WM-maintenance.

Repeated measures analysis with load (1 vs 3 target letters) and distraction (no target present versus target letter present but on the irrelevant diagonal) as within-subjects factors showed that a target letter on the irrelevant diagonal evoked prolonged RTs $[F(1,118) = 192.3, p < 0.001]$ and higher error percentage $[F(1,118) = 14.3, p < 0.001]$ compared with the non-target condition. No significant interactions between group and distraction were observed.

Prolonged RTs $[F(1,118) = 160.9, p < 0.001]$ and higher error percentage $[F(1,118) = 10.0, p < 0.01]$ were further observed when three target letters had to be remembered compared to a single letter. No significant interaction between group and load was observed for errors.

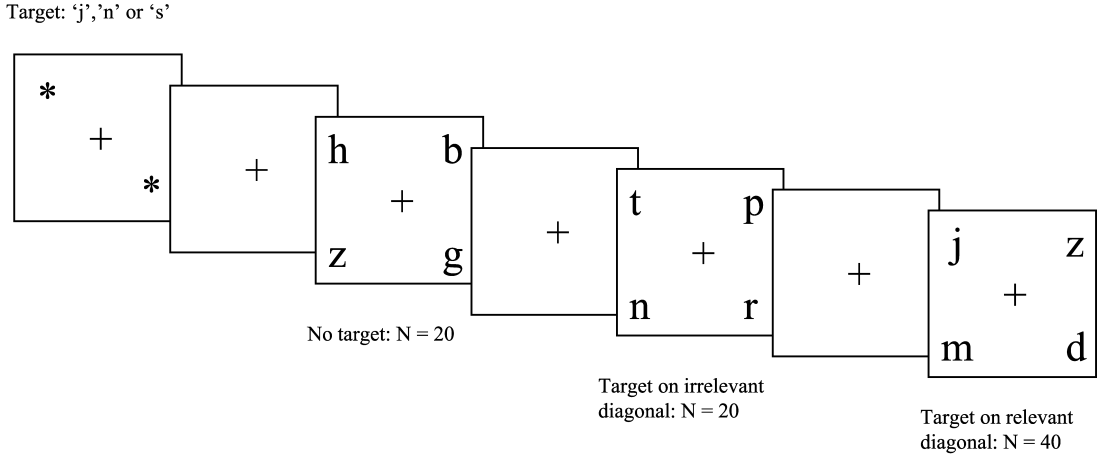

Fig. 2. Focussed attention: design.

Unexpectedly, there was a significant interaction between group and load for RT [$F(2,118) = 3.2, p < 0.05$]. However, the difference between controls and PKU patients became less when the number of items that had to be maintained in WM increased. A possible explanation for this result may be found in a combination of the low task demands of Part 1 of the task and generally slower speed of information processing in PKU patients. Controls may have been very fast in task Part 1 as a consequence of the low task demands, whereas PKU patients may have profited less from this. An increase of WM load may therefore manifest itself more in RT of controls compared with PKU patients whose baseline speed deficit does not increase in the second task part. Separate one-way ANOVAs for the load = 1 and load = 3-conditions confirmed that, while in the load = 1-condition the group difference in the no distraction-condition approached significance [$F(2,123) = 2.7, p < 0.07$], the group difference in the load = 3-condition was far from significant [$F(2,123) = 0.4, p > 0.6$].

The effect of group approached significance for RT [$F(2,118) = 2.8, p < 0.07$]. Contrast analysis showed a significant difference between controls and PKUhi patients (CE = -172.4, $p < 0.05$), whereas the differences between controls and PKUlo patients and between PKUlo and PKUhi patients did not reach significance. Groups differed significantly with respect to errors [$F(2,118) = 8.2, p < 0.001$]. PKUhi patients made significantly more errors than controls (CE = -1.9, $p < 0.001$) and PKUlo patients (CE = -1.2, $p = 0.05$). Controls and PKUlo patients did not differ significantly.

8.3. Flanker interference

The flanker interference task required subjects to focus on a central stimulus, while ignoring the surrounding stimuli (Fig. 3). The required response was linked to the colour of the central stimulus. When this central stimulus was blue, subjects were required to respond by pushing the left mouse button; when it was yellow, subjects had to respond by pushing the right mouse button. Filtering was measured by examining the differences in mean RT and error percentage between compatible flanker stimuli (the surrounding stimuli had the same colour as the central stimuli) and incompatible flanker stimuli (the surrounding stimuli had the interfering colour) in Part 2 of the task. Subjects had practised with the colour-hand conditions in Part 1 (which contained compatible and neutral flanker stimuli). Left- and right-hand response signal frequency was balanced, thus no response bias was induced.

The presence of interfering flankers produced prolonged RTs [$F(1,119) = 9.7, p < 0.01$] and higher error percentages [$F(1,119) = 10.3, p < 0.01$] compared with facilitating flankers. No interaction of 'flanker interference' with experimental group was observed, thus confirming the absence of deficient interference suppression in PKU.

For RT, a significant group effect was observed [$F(2,119) = 3.4, p < 0.05$], indicating significantly slower performance by PKUhi patients compared with controls (CE = -124.4, $p < 0.05$), whereas the difference between PKUlo patients and controls approached significance (CE = -109.8, $p < 0.08$). For accuracy, the effect of

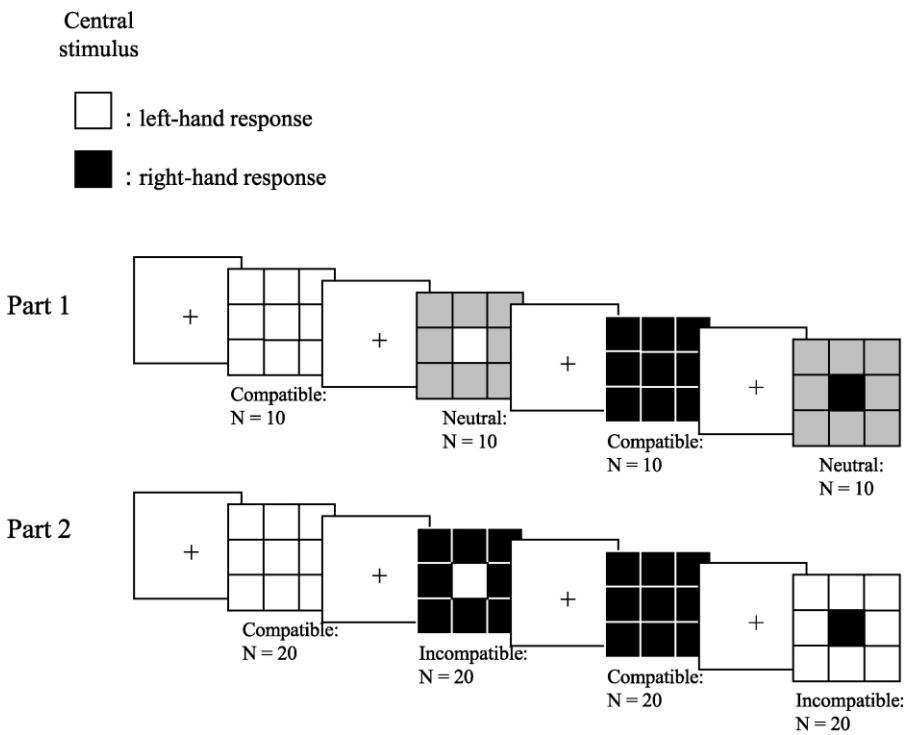

Fig. 3. Flanker interference: design.

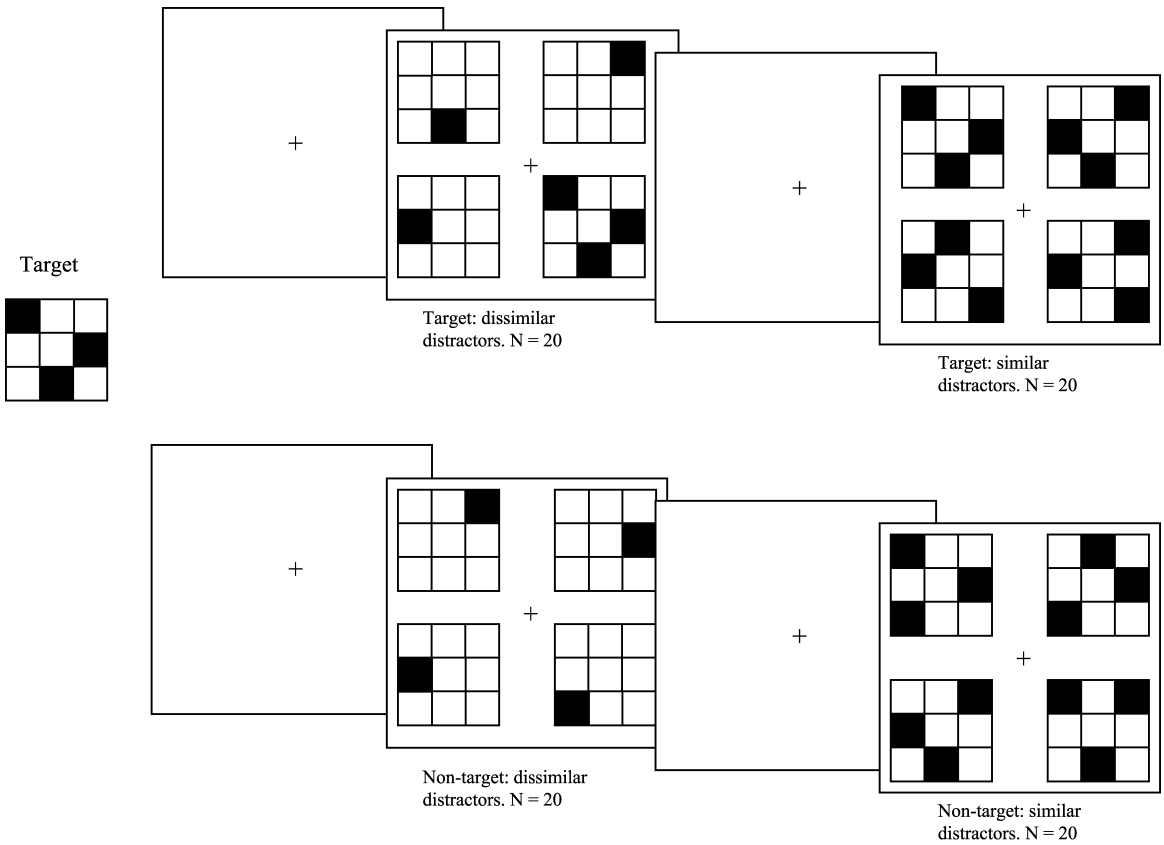

Fig. 4. Feature identification: design.

group was marginally significant [$F(2,119) = 3.0, p < 0.06$], with contrast analysis indicating a significant difference between controls and PKUhi patients (CE = -1.9, $p < 0.05$).

8.4. Feature identification

In this task, subjects searched a display consisting of four stimulus patterns for a target pattern. The target pattern remained the same throughout the task. Manipulation and monitoring of WM-content was examined by varying the degree to which the separate features constituting the target and distracter patterns had to be integrated/conjoined to reach a decision (Fig. 4). The similar condition, in which the distracter stimuli strongly resembled the target pattern, required top-down controlled search. In contrast, in the dissimilar condition, the distracters could readily be distinguished from the target.

The repeated measures analyses with as within-subjects factor the required level of feature integration (similar versus dissimilar) showed prolonged RTs [$F(1,119) = 1159.5, p < 0.001$] and higher error percentages [$F(1,119) = 108.7, p < 0.001$] when feature integration was required. A significant interaction with experimental group was observed for RT [$F(2,119) = 5.1, p < 0.01$], indicating that response speed increased more for PKU patients than for controls when feature integration was required (Fig. 5, left panel). For error percentage, a significant interaction between feature integration, group and age was observed [$F(2,119) = 4.7, p < 0.05$], indicating a stronger decrease of accuracy for younger PKU patients compared with controls of the same age when top-down controlled search was required. Such a difference was not observed for the older subjects (Fig. 5, right panel).

Significant effects of group were found for both RT [$F(2,119) = 4.6, p < 0.05$] and error percentage [$F(2,119) = 4.8, p < 0.05$]. There was a significant interaction between group and age for accuracy [$F(2,119) = 3.8, p < 0.05$]. Planned contrasts showed a significant difference in accuracy between controls and PKUhi patients (CE = -2.5, $p < 0.01$) and a marginally significant difference between PKUlo and PKUhi patients (CE = -1.9, $p < 0.08$). No significant difference was observed between controls and PKUlo patients. With respect to RT, a significant difference was observed between controls and PKUhi patients (CE = -274.4, $p < 0.01$).

Additional one-way ANOVAs confirmed that the group differences for RT (to the disadvantage of particularly PKUhi patients) were greater in the similar condition [$F(2,124) = 2.7, p < 0.08$] than in the dissimilar condition [$F(2,124) = 1.4, p > 0.2$]. For accuracy, group differences were marginally significant for both dissimilar

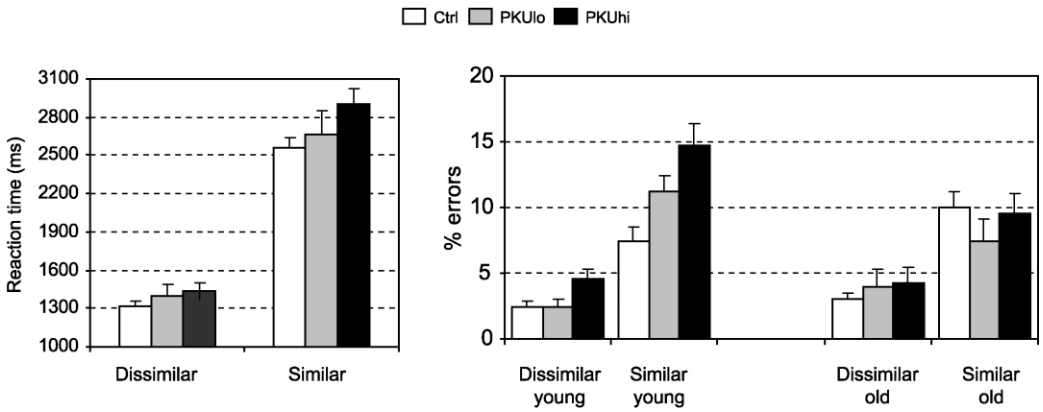

Fig. 5. Feature identification: effect of dissimilar and similar conditions on RT (left panel) and accuracy (right panel). PKUlo, concurrent Phe level ≤360 μmol/l; PKUhi, concurrent Phe level >360 μmol/l; Young, age < 11 years; Old, age ≥ 11 years.

$[F(2,124) = 2.6, p < 0.09]$ and similar signals $[F(2,124) = 2.8, p < 0.07]$. However, when only younger subjects were included in the analysis a large difference in F- and p-values resulted for dissimilar $[F(2,61) = 3.1, p < 0.07]$ and similar signals $[F(2,61) = 9.6, p < 0.001]$.

Controlling for mean RT in the baseline speed task (MRT_BS) changed the interaction between load and group in the focussed attention task from significant to marginally significant $[F(2,112) = 2.8, p < 0.07]$, which may be interpreted as support for our earlier explanation of RT-differences becoming smaller in the 'load = 3'-condition as a consequence of a stronger manifestation of a baseline speed deficit in the 'load = 1'-condition. The interaction between feature integration and group in the feature identification task for RT remained significant after controlling for MRT_BS $[F(2,118) = 3.4, p < 0.05]$, indicating that this specific manipulation affects task performance of PKU patients beyond general processing speed.

9. Discussion

PKU patients did not differ from healthy controls with respect to selective attention in visual search (orienting). The results of previous studies clearly suggest vigilance impairments in treated PKU patients [11,23,44,100]. Impairments of executive control appear to be restricted to tasks requiring inhibition of prepotent responding [32,44,45,116,118] and to tasks requiring top-down controlled visual search (the present study). No specific deficits were observed when subjects were required to selectively attend to a specific part of a stimulus display and ignore distracters in other parts of the display, as was shown by the absence of significant interactions between group and distraction in the focussed attention and flanker tasks. Performance of PKU patients did not disproportionately deteriorate compared with controls when WM-load increased. Thus, the maintenance-function of WM appears to be unaffected. It has, however, been argued that, when load exceeds a certain maximum, mnemonic processing no longer suffices for adequate task performance, and subjects need to adopt specific monitoring strategies [99]. Future investigations should point out whether this aspect of manipulation and monitoring of WM-content is affected in treated PKU.

When perceived as a simple pattern/object recognition task, it may be argued that the feature identification task, which showed substantial differences between controls and PKU patients, does not require manipulation of WM-content. Such tasks activate the medial temporal lobe [72,92]. Pattern recognition in the 'similar' (i.e. difficult) trials of the feature identification task, however, required continuous monitoring of the target configuration in WM and the separate features of the presented stimulus patterns had to be integrated to produce a correct match or mismatch. Levy and Golman-Rakic [52] argued that objects in WM-tasks can be defined by subjects in accordance to spatial relations among their features. It is likely that establishing the spatial relations between the separate features of the target and signal patterns in the feature identification task contributes to task performance. Nevertheless, establishing spatial relations among the separate features of target and distracter patterns classifies as a manipulation-function of WM, engaging similar brain areas (DLPFC) as manipulation of objects in WM [23,27,73,74].

The pattern of results was further substantiated by our findings in a diet intervention study [43]. Patients whose Phe levels had decreased at the second assessment showed significant improvements compared with controls and patients whose Phe levels had increased. The greatest improvements were observed when sustained attention, inhibition of prepotent responding, and top-down controlled visual search were required.

The vigilance and executive control deficits found in our studies were most evident in the younger subjects (age < 11 years). This is consistent with the results of

a number of recent studies showing the absence [42,57] or decline [115] of cognitive deficits in adolescents with PKU, who had been under good dietary control throughout the first decade of life and support the present treatment guidelines in most countries. These guidelines [12,65,70] generally suggest a severe Phe-restricted diet until early adolescence, after which a gradual relaxation of the diet is allowed. When deficient task performance was found for adolescent patients, no influence of concurrent Phe was observed. This may indicate more structural deficits, associated with Phe levels earlier in life. Diamond and Herzberg [31] found that impaired visual contrast sensitivity in PKU patients was not related to concurrent Phe level, but to Phe levels during the first month of life, during which the visual system rapidly matures. In a study with PKU siblings [30], it was found that the older siblings (in whom PKU was detected postnatally and who had started the Phe-restricted diet at about $1\frac{1}{2}-2$ weeks of age) showed poorer contrast sensitivity than younger siblings (in whom PKU was detected prenatally and who had started the diet by 2 or 3 days of age). We found [44,45] for PKU patients stronger relationships of sustained attention and manipulation-functions of WM with Phe levels during age periods with a rapid development of executive abilities [38,56,117] than with concurrent Phe level.

One of the most important findings in this study is that interference suppression and response inhibition are not similarly affected in PKU patients, thus supporting a dissociation between these executive control functions. DLPFC-involvement may differ between tasks requiring response inhibition and top-down controlled visual search, and tasks requiring filtering, particularly when the information that needs to be maintained on-line is practised with and remains unchanged [18]. Although interference suppression and conflict resolution have been related to VLPFC- and ACC-activity [9,18,59], DLPFC-involvement in these operations has also been demonstrated [81]. The PFC-dysfunction hypothesis for PKU [32,118] states that prefrontal dopaminergic neurons are disproportionally sensitive to fluctuations in tyrosine (Tyr), since they lack the synthesis-modulating autoreceptors present in other brain areas and consequently have a faster breakdown rate than other dopaminergic neurons. Based on this hypothesis, PKU patients would be expected to show deficient interference suppression and conflict monitoring as well. One possible explanation would be that interference suppression tasks are less sensitive to catecholaminergic innervation of DLPFC [55,95]. In addition, response inhibition may require different DLPFC-connections with other cortical or subcortical structures compared with interference suppression. Different pathways may show varying sensitivity to neurotransmitter modulation, or sensitivity to modulation of different neurotransmitters [39,95].

10. Neurotransmitters

Evidence has been provided for a relation between acetylcholine and orienting attention, noradrenaline and vigilance/sustained attention, and dopamine and executive control [36]. In an experimental animal model of treated PKU, Diamond and colleagues [29] found a reduction of dopamine and dopamine metabolite HVA in the prefrontal cortex but not in other brain regions. This was accompanied by and correlated with impairment on a delayed alternation task. For humans with PKU, decreased levels of monoamine neurotransmitters (serotonin, noradrenaline, and dopamine) and their metabolites have also been reported in cerebrospinal fluid [49,50,54]. McKean [64] observed decreased monoamine neurotransmitter levels in autopsied brains of PKU patients. Krause et al. [50] reported an inverse relationship between plasma Phe levels and urine dopamine and serotonin excretion, accompanied by a positive correlation between plasma Phe and an executive control task (i.e. a dual-task requiring inhibition of prepotent responding).

Dopamine availability has been found to influence some cognitive functions mediated by PFC but not others. McDowell, Whyte, and D'Esposito [63] administered dopamine agonist bromocriptine to patients with traumatic brain injury with lesions in prefrontal areas. Neuropsychological task performance requiring manipulation and monitoring of WM-content (dual-task, trailmaking test B, Stroop, Wisconsin card-sorting test, FAS test) improved. In contrast, task performance requiring maintenance of WM-content (verbal span task, spatial delayed response) and control tasks considered independent of prefrontal cortex function (trailmaking test A, single-task conditions from the dual-task paradigm, Stroop-control, bi-letter cancellation test) did not improve. The effects of bromocriptine administration on the spatial delayed response task, however, are mixed. Luciana and Collins [55], for example, found that bromocriptine improved performance of healthy subjects on this task, whereas haloperidol (a dopamine antagonist) impaired performance. Kimberg, D'Esposito, and Farah [48] found no effects of bromocriptine on spatial delayed response in healthy subjects. These authors further reported that bromocriptine only improved performance on prefrontal measures in subjects with lower WM capacity, whereas it impaired performance in subjects with higher WM capacity. The results suggest that the effect of a specific neurochemical agent depends on the type of cognitive operation and on individual differences.

These two factors were also emphasised by Robbins [95] in his review on chemical neuromodulation of frontal-executive functions. Robbins further stated that the effect of specific chemical agents depends on which PFC-projection is targeted by the specific chemical agent. Different PFC-projections, including those to the dopamine-containing cells of the ventral-tegmental area, the noradrenergic neurons of the locus coeruleus, the serotonergic neurons

of the raphé nuclei, and the cholinergic neurons of the basal forebrain [39], could all be important for efficient performance of tasks requiring strategic processing, but could modulate performance in different ways. Several studies have shown that NE and DA agents influence performance on the same tasks [3], for instance RVIP [20], extra-dimensional set-shifting and the more complex components of the Tower of London and a spatial WM task [68]. Mehta and colleagues [66] recently showed that methylphenidate (MPH, which increased NE and DA concentrations) selectively influenced performance of a spatial WM task through changes in the posterior parietal cortex and DLPFC. The spatial WM-task required subjects to search for blue tokens hidden behind red circles. The stimulus array consisted of six ('easy') or 12 ('difficult') red circles and subjects were instructed that, once a blue token had been found behind a particular red circle, that circle would not be used again to hide the token. Thus, subjects had to remember the circles where a token had been detected on previous trials and were required to resist searching behind them on subsequent trials. The results indicated that the online storage and retrieval of information from posterior cortical association systems were influenced by noradrenergic modulation, through MPH, of the posterior parietal cortex, whereas inhibition of previously successful selections was influenced by dopaminergic modulation of DLPFC [66]. This study also illustrates how performance of complex neuropsychological tasks may be influenced by neurochemical modulation through different PFC-projections. Maintaining information on-line and retrieval of information from posterior association cortices engages (ventrolateral) PFC [74,82]. Based on evidence for different functional properties of a dorsal system (which includes parts of the intraparietal cortex) and a ventral fronto-parietal system [18], it may be hypothesised that these circuits have different neurochemical properties.

In addition to individual differences and the possibility that different PFC-projections influence (specific) aspects of cognition, dosage of a neurochemical agent could be critical. Adverse effects of administering catecholamine agents, possibly caused by overdosing the target structure or other structures influencing task performance with sufficient dopamine and noradrenaline, have frequently been reported [33,97,111].

Tyrosine (which is included in the amino acid supplements PKU patients take), the metabolic precursor of dopamine and noradrenaline, has been shown to influence executive control functions in a number of different syndromes [112]. In PKU patients, however, the effects of administering (extra) tyrosine are inconclusive. In some studies beneficial effects have been reported on speed of information processing of PKU patients on unrestricted diets [54,58]. In other studies, with patients who were on relaxed diets [85], patients who had not stayed on dietary treatment consistently [107], or patients on a relatively strict diet [60], no beneficial effects were found. Supplementation of tyrosine as part of LNAA treatment, with various combinations of LNAAs except Phe (tyrosine, tryptophan, methionine, leucine, isoleucine, valine and histidine) appears to be more promising [51,84].

In view of the evidence that catecholamine modulation specifically influences manipulation functions of WM through 'fronto-striatal loops' [1,4,63,67,95], it could be argued that to improve the neuropsychological impairments of PKU, this pathway should be specifically targeted. However, untreated adult patients did not seem to profit from L-DOPA administration [113]. This possible treatment strategy could, however, be investigated in early and continuously treated patients. Varying dosage and other agents targeting the fronto-striatal pathway with different compositions may provide further options for a treatment strategy.

Serotonin, which has also been found to be lowered in PKU, appears to influence different types of tasks, in particular those mediated by the orbitofrontal cortex. Examples of tasks appealing to the orbitofrontal cortex are those requiring reversal shifts (reinforcement) and decision-making. Park, Coull, McShane et al. [76] showed, in monkeys, impaired learning of paired associates after tryptophan depletion (tryptophan being the metabolic precursor to serotonin), but no effects on performance of self-ordered spatial WM and a planning task. Rogers et al. further reported impaired reversal learning [97] and impaired decision making ('gambling') [98] after serotonin reductions in humans. In PKU, no specific attentional deficits associated with serotonin reductions have been investigated.

In summary, the findings show deficiencies in treated PKU in vigilance and specific aspects of executive control, i.e. inhibition of prepotent responding and top-down controlled visual search. No differences with controls were found for selective attention in visual search, WM-maintenance, and interference suppression. Manipulation and monitoring-functions of WM have been shown to be mediated by the mid-dorsolateral PFC, but only a number of these functions have been shown to be susceptible to catecholamine modulation (through the frontostriatal pathway). Whether catecholamine modulation produces a positive effect depends on a number of factors, such as individual differences, which PFC-projections are targeted, and dosage.

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