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Thesis

Selective impairment in executive functions: a test of the selective executive deficit hypothesis in adults with treatment-discontinued Phenylketonuria

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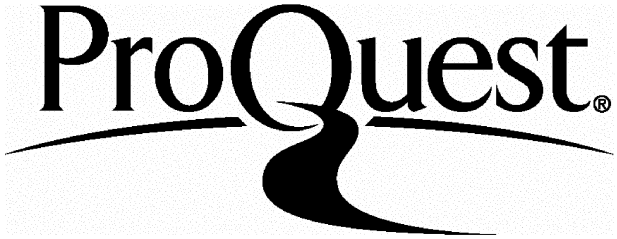

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ABSTRACT

Executive functions are processes involved in the everyday control of thoughts and actions and have been linked to the prefrontal cortex. Recent models of cognitive functioning in Phenylketonuria (PKU) have linked it to selective impairment in executive functions due to depleted dopamine levels in the prefrontal cortex. This is caused, in part, by elevated levels of Phenylalanine in the blood. Dopamine is thought to play a central role in functions linked with the lateral prefrontal cortex and associated pathways. The selective executive deficit hypothesis of PKU suggests that measures that place high demands on active working memory and sustained attention are likely to be sensitive to any impairments mediated by dopamine depletion. These functions have been linked to the dorsolateral prefrontal cortex, which is particularly sensitive to fluctuations in dopamine in the brain.

This study compared performance of a group of treatment-discontinued adults with PKU to a group of healthy controls matched for age, sex, IQ and educational background on tasks sensitive to dorsolateral prefrontal cortex functioning, in comparison to another test of executive functioning, reward-based learning, and a control task, considered to make minimal demands on executive functions. Adults with PKU were shown to be selectively impaired on tasks requiring monitoring of information in the context of processing of higher working memory loads, but not on the alternative executive task or the control task, in comparison to healthy control participants.

1.0 INTRODUCTION

Summary

Phenylketonuria (PKU) is a disorder which affects dopamine levels in the brain. The aim of this study is to establish whether adults with treatment-discontinued PKU display selective executive impairments in tasks with a high attention and working memory load, in accordance with selective executive deficit hypothesis of PKU. Although aspects of this hypothesis have been supported by evidence from a handful of published studies with children & adolescents, it has not been thoroughly tested in adults with untreated PKU. From a clinical perspective, this is relevant to those suffering with PKU who remain unsure whether to return to the burdensome dietary treatment and clinicians have little evidence-base from which to advise them. Additionally, from a theoretical perspective, evidence of selective executive deficits in this population is important for the evaluation of recently-developed theories of aspects of executive functioning and their anatomical and neurochemical basis. Evidence of selective executive deficits may also help to shed light on possible dissociations between different functions and may therefore inform theories of executive functioning.

1.1 PHENYLKETONURIA (PKU)

In this section the clinical presentation, treatment, and neurobiological basis of the disorder, Phenylketonuria, will be described. Furthermore, evidence on the outcome of treatment, with respect to cognitive functioning, will be assessed with reference to a recent hypothesis which attempts to explain the pattern of selective executive

impairments in PKU. In summary, this hypothesis suggests that dopamine neurotransmission in PKU is impaired and that this has a particular impact on the dorsolateral prefrontal cortex, where neurons are especially sensitive to mild fluctuations in dopamine. Thus, it is argued that altered modulation of dopamine in the dorsolateral prefrontal cortex may be the neurobiological basis of the particular deficits apparent in PKU.

1.1.1 Importance of early diagnosis and treatment of PKU

Phenylketonuria (PKU) is a relatively common hereditary metabolic disorder, with an incidence of approximately 1 in every 10,000 newborn infants (Güttler, 1988). It was first described clinically by Folling in 1934. PKU is believed to be caused by a mutation of a gene on chromosome 12 (Woo, Lidsky, Güttler, Chandra & Robson, 1983) which leads to a deficiency of the enzyme Phenylalanine hydroxylase (PAH). PAH converts the amino acid, Phenylalanine (Phe) into another amino acid, Tyrosine (Tyr) which is a precursor of dopamine. This deficiency results in excessively high levels of Phe in the blood and depleted levels of dopamine, which is important in neurotransmission.

In people with untreated PKU, blood Phe levels can rise to over 10 times normal levels (Diamond, Prevor, Callender & Druin, 1997). The toxic effects of such high Phe levels and restricted supply of dopamine to the brain results in irreversible severe mental retardation which becomes evident within the first year of life. Intelligence of those with untreated PKU tends to plateau from around the age of 3 and adults typically achieve IQ's in the 'extremely low' range of intellectual functioning. In

addition to severe mental retardation, untreated individuals with PKU have also been shown to manifest a range of behavioural impairments, including hyperactivity, attention and perceptual-motor problems, aggressiveness, negative mood, and motor disturbance (MacLeod, Munro, Ledingham & Farquhar, 1983; Paine, 1957; Primrose, 1983). Cognitive and behavioural problems seen in late-treated children are similar but less extreme (Margolin et al., 1978; McKean, 1971). Thus, the specific cognitive impairments of untreated and late-treated PKU appear to be related mostly to executive function processes, such as problem-solving, attention, and perceptual-motor functioning, than to non-executive function processes.

Effective screening for the disorder in newborn infants became possible from around 1970 with the introduction of the blood spot bacterial inhibition test (Guthrie & Susi, 1963). If diagnosed with PKU, newborn infants are usually started on treatment within the first month of life. Treatment consists of a specially formulated diet with the aim of reducing the level of blood Phe to an acceptable range, which varies according to age (Medical Research Council, 1993b). The amount of natural protein in the diet is severely restricted so as to reduce further intake of Phenylalanine. The diet is supplemented with low protein food substitutes and Phe-free amino acids, vitamins and minerals to ensure well-balanced nutrition is maintained despite the restrictions of the diet.

At present, UK guidelines indicate that blood Phe should rise to no more than 5 times the normal levels in order to protect the developing brain (Medical Research Council, 1993a). Regular monitoring of blood Phe levels is necessary to establish whether levels are being maintained within the acceptable range. This is done by people at

home using a finger-prick blood spot onto a strip which is sent into the laboratory. The clinical team check the person's blood Phe levels and also try to ensure that the person is maintaining a well-balanced diet in other respects.

1.1.2 Duration of dietary treatment

The age at which it is recommended that people can come off the diet has increased progressively to 8, 10, 12 and 16 years of age, as evidence emerged about some negative effects of stopping diet. In Britain, there is now a 'diet for life' policy. Policies have also changed with regard to the optimal blood Phe level at which a person maintained on diet should aim to achieve. Current U.K. guidelines now recommend upper limits of blood plasma Phe at 360 μmol/L for young children, 480 μmol/L for school-age children, and 700 μmol/L for adolescents above school age and adults (Medical Research Council, 1993b). Although medical advice has changed over the years in the light of new evidence, many people were previously advised to come off the diet in adolescence and they continue to remain untreated in adulthood. Given that it has been many years since these people have been on the diet, many are poorly motivated to return to the restrictions of the diet, even though clinicians now tend to advise people that it may be safer for them to go back on.

1.1.3 Outcome in PKU

Early screening and effective dietary treatment beginning in the first month of life have altered the outcome of PKU considerably. Children who are treated early can now expect to go to mainstream schools and achieve normal developmental milestones. In evaluating the success of dietary treatment, studies have typically used standardised scales of general intelligence such as the Stanford-Binet scales and the Wechsler scales. Evidence accrued using IQ scores as an outcome measure suggests that children with early and continuously-treated PKU typically achieve IQ scores within the normal range (e.g. Holtzman, Kronmal, van Doorninck, Azen & Koch, 1986; Koch, Azen, Friedman & Williamson, 1982, 1984). However, the IQ scores of both children and adults with early-treated PKU typically remain lower than their parents and unaffected siblings, and lower than the mean of the general population (Berry, O'Grady, Perlmutter & Bofinger, 1979; Dobson, Kushida, Williamson & Friedman, 1976; Hudson, Mordaunt & Leahy, 1970; Koch et al., 1984; O'Flynn & Hsia, 1968; Williamson, Koch, Azen & Chang, 1981).

However, when treatment was first introduced it was not clear for how long it should be continued. Initially, dietary therapy was stopped at 5 years of age, but it later became apparent that this was not sufficient to prevent cognitive impairment. Larger scale studies found a relationship between length of time on diet and IQ scores. For example, the North American Collaborative Study examined a cohort of early-treated children with PKU over several years using standardised IQ scales. At the age of 4 years, they found that the mean IQ of children with PKU was 93 (using the Stanford-Binet Intelligence Scale), with those beginning treatment earlier having higher IQ

scores (Dobson, Williamson, Azen & Koch, 1977). At the age of 8 years, IQ was on average 100 for the children with PKU compared to 107 for their non-PKU siblings (using the Wechsler Intelligence Scale for Children) (Koch et al., 1984). At the age of 12 years, further assessment showed that IQ scores correlated with dietary control (Smith, Beasley & Ades, 1990).

In the UK, the PKU registry has produced similar data, suggesting that patients with PKU on average have IQ scores that are 4 points lower for each month's delay after birth until treatment onset for each 300 μmol/L rise in average blood Phe level (Seashore, Friedman, Novelly & Bapat, 1985). Thus, treatment history, dietary status and blood Phe levels are all important indicators used to indirectly estimate the extent to which this disorder is having a deleterious impact on the brain. Furthermore, on the basis of neurological investigations, small white matter abnormalities have been identified, even in early and continuously-treated individuals with PKU, but there is little evidence of any other lasting neurological damage (Lou et al., 1992). In summary, it has been well established that early diagnosis and continuous careful treatment of PKU with a well-controlled diet is essential in order to secure the best possible outcome.

1.1.4 Social and emotional functioning in PKU

Most of the evidence on social and emotional functioning in PKU has a developmental focus and is based on studies with children and families. Thus, there is little evidence on such aspects of outcome in adults. A review of the studies with children and adolescents suggests that early and continuously-treated children do not show a higher risk for emotional and social problems (Sullivan, 1999; Weglage et al., 1996), but that they do appear to be more likely to experience cognitive problems such as poorer concentration, but without the negative social behaviour seen in disorders such as Attention-Deficit Hyperactivity Disorder (Kalverboer et al., 1994). However, some studies have suggested that parents feel that their parenting style is affected by the disorder. Parents have described difficulties with issues such as their need to be protective about what is eaten by their children, helping their children cope with feeling different from others and with the practical stresses associated with having to maintain a restrictive diet and take regular blood tests for example (Hendrikx et al., 1994).

There is also evidence of difficulties with regards to adolescents. There is some evidence that adolescents with early and continuously-treated PKU show a greater vulnerability to psychiatric disturbance and psychosocial problems, which they describe as stress resulting from the burdensome diet (Weglage et al., 1996). Furthermore, adolescents with PKU have been shown in one study to be characterised by less autonomy, a greater likelihood of making a negative evaluation of their scholastic ability, less achievement motivation, low frustration tolerance, a generally more negative self-description and feeling of being 'not quite healthy' in

comparison to their non-PKU peers (Weglage et al., 1992). It is interesting to note that there has been found to be no evidence of an association between mean blood Phe level over the first 13 years of life and level of disturbance in 13 year old adolescents (Burgard, 1994). Instead these difficulties may be mediated by the problems maintaining dietary compliance during adolescence, when the need to be seen as 'fitting in' with the social peer group appears to exercise a greater impact on behaviour (Zemen et al., 1996). The problems described may also be influenced by stressors associated with having a chronic disorder, rather than having PKU in particular, which could be examined further in studies where functioning is compared with age-peers with different chronic disorders affecting their health. Thus there are several issues which have not yet been explored in the published literature to date.

1.1.5 The executive deficit hypothesis of PKU

Direct measurement of cognitive functioning with IQ tests appears to have been the simplest means of measuring outcome for people with PKU. However, the reliance IQ as an index of outcome may have underestimated the effects of PKU in early and continuously-treated individuals, since IQ tests such as the Wechsler scales are known to be relatively insensitive to impairments in 'executive' functions. Executive functions are processes involved in the everyday control of thoughts and actions, and have been linked to the prefrontal cortex (PFC) of the brain.

Recent models of cognitive functioning in PKU have linked it to selective impairments in executive functions (Diamond, Ciaramitaro, Donner, Djali & Robinson, 1994; Pennington, van Doorninck, McCabe & McCabe, 1985; Welsh,

Pennington, Ozonoff, Rouse & McCabe, 1990; 1996) such as in monitoring information with a high working memory load, attentional and inhibition processes (Diamond et al., 1997; Weglage, Schmidt, Fünders, Pietsch & Ullrich, 1996; Welsh et al., 1990). In general, research has found basic language, perception, memory and gross-motor functions to be normal in individuals with early-treated PKU. However, there is substantial evidence of executive deficits in early-treated children with PKU. These have demonstrated deficits in attentional and working memory processes, and speed of information processing (Brunner, Berch & Berry, 1987; Diamond et al., 1997; Faust, Libon & Pueschel, 1986; Krause et al., 1985; de Sonneville, Schmidt, Michel & Batzler, 1990; Welsh et al., 1990).

Several authors have put forward an explanation for these apparent selective executive deficits in children with early and continuously treated PKU (Diamond et al., 1997; Weglage et al., 1996; Welsh, 1996). These authors have argued that dopamine neurons in the ventral tegmental area projecting to the PFC are differentially sensitive relative to a mild reduction in Tyr compared to other dopamine neurons in the brain. Tyr is the precursor of dopamine. Most brain regions receiving dopaminergic input are unaffected by small changes in Tyr levels within the Central Nervous System (CNS). Dopamine neurons that project to the PFC fire more rapidly and turn over dopamine more quickly than other parts of the brain (Bannon, Bunney & Roth, 1981; Tam, Elsworth, Bradberry & Roth, 1990; Theirry et al., 1977; Wurtman, Hefti & Melamed, 1981). Thus, in PKU increased Phe levels are thought to impede the transport of other amino acids to the brain. This in turn leads to selectively depleted dopamine levels in the PFC, which can result from even modest elevations of Phe. This is argued to have the greatest impact on neurons in

the lateral PFC due to their special characteristics (Bannon et al., 1981; Bradberry, Karasic, Deutch, & Roth, 1989; Diamond, 1998; Thierry et al., 1977).

Diamond (1998) has argued that evidence from animal studies supports this theory as it demonstrated impairments in the ability to make a delayed response (which requires working memory) when blood plasma Phe levels were experimentally raised (Diamond et al., 1994). This is similarly found with ablation of the prefrontal cortex (e.g. in rats Bubser & Schmidt, 1990; Larsen & Divac, 1978; Wikmark, Divac & Weiss, 1973; in monkeys Bättig, Rosvold, & Mishkin, 1960; Jacobsen & Nissen, 1937; Kubota & Niki, 1971). As predicted, lower levels of dopamine and the dopamine metabolite, HVA, were found in the PFC in PKU-model animals compared to controls. This is supported by earlier work built on modelling the untreated PKU condition (Brass & Greengard, 1982; Greengard, Yoss & DelValle, 1976).

Given this explanation for executive deficits in patients with PKU, levels of Phe in the blood may be expected to be associated with extent of cognitive impairment, with higher levels being related to poorer functioning. Although several studies have demonstrated such a relationship (Diamond et al., 1997; Pietz et al., 1998; Ris, Williams, Hunt, Berry & Leslie, 1994; Smith, Klim, Mallozzi & Hanley, 1996; Weglage et al., 1996; Welsh et al., 1990), others have not (Griffiths, Campbell & Robinson, 1998; Griffiths, Tarrini & Robinson, 1997).

However, there are several factors confounding the comparison between different studies. Firstly, due to differences in age between different samples, and the fact that

there are different levels of blood Phe recommended for different age groups, comparing blood Phe levels between different samples studied is not straightforward. Furthermore, the effects of blood Phe levels on cognitive performance is complicated by levels of IQ, the age at which diet was started and stopped, the level of adherence to diet, and individual differences in the extent to which dietary control is able to reduce blood Phe levels. For example, treatment continuity has been shown to make a difference to problem-solving ability (Brunner, Jordan & Berry, 1983) and reaction times (Krause et al., 1985; Lou, Lykkeluind, Bruhn & Niederwieser, 1987; Schmidt et al., 1994), but there are exceptions to this (Jordan et al., 1985). Blood Phe levels have been shown to be more strongly related to performance than IQ (Diamond et al., 1997; Welsh et al., 1990). However, the lower the IQ, the less the effect on performance after reducing Phe levels (Krause et al., 1985). Additionally, there is some evidence to suggest that cognitive impairments in adults are mediated in part by lifetime blood Phe levels (Pietz et al., 1998; Ris et al., 1994; Smith et al., 1996). For example, Pietz et al., (1998) demonstrated that both concurrent Phe levels and Phe levels from the age of 12 onwards were related to performance on an attention task. It may be the case that for adults with PKU lifetime blood Phe levels bear a closer relationship to performance than concurrent blood Phe levels. This may be because when concentration of Phe in the blood reaches a saturation point, which varies between individuals, there are additional toxic effects of the accumulation of Phe (Seakins, Ersser & Hjelm, 1982). This may make concurrent blood Phe levels less straightforward as an indication of the extent of effect of high Phe levels on the brain.

The equivocal findings on this issue of the relationship between blood plasma Phe levels and cognitive performance is further complicated by the fact that blood Phe

levels are only an indirect measure of brain Phe levels (see e.g. Koch et al., 2000) and the technology to measure brain Phe levels directly is still being developed. However, stopping the diet or Phe loading has been shown to lead to decreased levels in the neurotransmitter metabolite 5-HIAA (Lou et al., 1985) and dopamine (Krause et al., 1985) in patients with PKU. These decreases have been shown to be related to slower reaction times on tests of sustained attention and higher integrative functions. There is a body of evidence supporting the conclusion that a decrease in sustained attention ability may be due a decrease in neurotransmitter synthesis.

Overall, there are only a handful of studies investigating selective deficits in adolescents and adults and so far these findings have been more mixed (Clarke, Gates, Hogan, Barrett & MacDonald, 1987; Griffiths et al., 1998b; Mazzocco, Nord, van Doorninck, Greene & Kovar, 1994; Ris et al., 1994; Smith et al., 1996; Stemerdink et al., 1994). Group differences have been found in some studies but not in others. There are several factors which complicate the comparison of these different studies. Firstly, the samples have varied in age, gender, IQ and dietary history, all of which could affect task performance (Waisbren, Brown, de Sonneville & Levy, 1994). Secondly, the studies have employed a variety of measures. Some of the measures used have not been well-validated by previous research as good measures for tapping particular aspects of executive functioning, nor as reliably associated with functioning of the lateral prefrontal cortex. Thirdly, many studies have employed very small sample sizes, which can affect statistical power, and therefore the validity of the findings.

In summary, the selective executive deficit hypothesis of PKU predicts that the neurochemical changes in PKU are associated with particular impairments in

executive functions which are linked to the lateral PFC of the brain, such as attention and manipulation of information with a high working memory load. There are several studies based on children with PKU which have confirmed this prediction, but the evidence in adults is more mixed. This may be due, in part, to the difficulty measuring performance on tasks which can tap particular aspects of executive functioning, and the relative lack of well-controlled studies in this area. In addition, such cognitive impairments have been shown to be associated with high blood plasma Phe levels, which are an indirect measure of brain Phe, but the findings with regards to this relationship are also equivocal.

1.2 EXECUTIVE FUNCTIONING

Executive functions are higher, goal-directed mental activities that are organisational and supervisory in nature and heavily dependent on good attentional control. They entail planning, selecting or maintaining complex behavioural routines, often in novel contexts (Kelly et al., 1996). The term 'executive' is derived from Baddeley's (1986, 1999) model in which a 'central executive' plays a major role in attention, planning strategies, co-ordinating behaviour and the suppression of irrelevant information. According to this model the central executive integrates information from other sources within the brain and it has an over-arching co-ordination function for different processes, but does not store information (Richardson, 1996a, 1996b). In everyday activities the central executive helps a person decide what to do and enables them to keep focused towards achieving a particular goal. This has some similarities to Shallice and Burgess's (1991) conceptualisation of a 'supervisory system' which helps a person decide which issues deserve attention and which should be ignored.

Such processes may be used in deciding how to tackle a problem, selecting an appropriate strategy and monitoring ongoing performance. This is especially important when a person is tackling a novel problem or situation.

There has been a continuing debate about whether there is such a unitary system or whether 'executive' processes are heterogenous in nature and function. This has led to attempts to define what can be considered 'executive' versus 'non-executive' processes. The criteria for making such a definition has long been discussed in the literature and some have even argued that what others describe as executive processes are simply descriptions of task demands. Thus the construct validity of using the term 'executive' to describe cognitive processes has been questioned (Burgess, 1998). Yet there is some agreement that the term executive is a way of describing behaviour in novel situations, where automatic control of behaviour on the basis of past experience cannot be used, where allocation of attentional resources allowing sustained attention or divided attention between different tasks is necessary, and in the prevention of responses that are inappropriate in a particular context (Rabbitt, 1998).

The frontal lobes, particularly the PFC, and associated pathways are believed to be central to our ability to respond adaptively to the environment in a goal-directed manner, which involves such executive functions (see e.g. Norman & Shallice, 1986). Poor judgement, planning and decision-making were recognisable characteristics in people with damage to the PFC, yet it has been difficult to conceptualise the psychological processes which contribute to these complex cognitive capacities. For example, as mentioned above, Baddeley has conceived of a

Central Executive which has an overall control and monitoring function which processes inputs from two slave systems; the phonological loop and the visuo-spatial scratchpad (Baddeley, 1996). Shallice and Burgess (1993) have described a Supervisory System which is used purely for coping with novel situations, in comparison to Contention Scheduling processes which control more habitual behaviours. Alternatively, Domasio (1996) has described a Somatic Marker hypothesis in which a stimulus sets off a somatosensory pattern which boosts attention and working memory. This in turn triggers associations on the basis of previous experience which are integrated in reasoning and decision-making processes.

There are also models of executive processes which are intricately linked to the cortical architecture which is believed to be involved. These researchers have drawn on existing evidence from animal and human studies to identify dissociations between different brain regions and systems of neuronal and neurochemical activity. These are argued to be evidence for dissociable executive processes, such as Petrides' (1994) distinction between monitoring and active retrieval of information, or Rolls' (1999) theory about the role of the orbitofrontal cortex in reward-based learning, given its links to the striatum which is implicated in neurochemical modulation. There is no general consensus about the most valid approach to understanding such cognitive processes and this is an area of continuing active debate.

To help examine evidence for these different explanations of how such functions are carried out by the brain, theorists in the field of cognitive neuropsychology have

drawn upon evidence from a variety of sources. These include both animal and human experiments involving lesions, brain imaging, electrophysiological and neurochemical recordings. Studies in the field of human neuropsychology have been focused on the fractionation of executive processes, which are argued to be subserved by particular regions of the frontal cortex. One paradigm employed is examining how particular brain lesions of the PFC in humans and primates can disrupt their performance on a range of executive tasks (see e.g. D'Esposito & Postle, 1999). In such studies behaviour and electro-physiological activity of particular neurons are measured. The results are used to draw conclusions about the specific ways in which areas of the brain are associated with inability to carry out tasks which are hypothesised to demand the operation of specific cognitive processes. From observations of ability to perform a particular task, but not another, theories are derived about dissociations between cognitive functions and associated brain regions (Rabbitt, 1991).

Much of the recent evidence on localisation within the PFC is also based on functional imaging work. In these studies, the brain is scanned for patterns of activation whilst the subject of the experiment performs a particular task. In deriving theories of cognitive functioning and activity in the PFC, imaging and lesion studies rest on the assumption that a task taps a particular cognitive operation or process. However, there has been considerable debate about such processes and whether it is valid to discuss functional independence when it comes to so-called 'executive processes'. Some researchers have taken a 'local approach' in which they look for consistent patterns of activation across individuals which they argue can be generalisable. Others take a 'global approach' by looking at widespread activation

and inconsistencies in areas of activation that may show that some tasks have a set of common lower-order task demands that prompt activation of these areas or shared areas of activation which suggest a broader functional conceptualisation of how the brain works. Alternatively, others have used a 'network approach' to study the pattern of interactions across areas of the brain, which they argue are mores significant than looking at each brain region separately.

There are methodological difficulties in all the methods described. For example, associations between brain activation and cognitive processes do not provide direct evidence of causation. Also task demands may be associated with certain cognitive processes but this rests on an assumption that a particular task taps a particular cognitive process or function. One way of improving the strength these assumptions is to use lines of converging evidence from different methodologies but which are suggesting similar interpretations. For example, where patterns of preserved and impaired performance in a task have been shown to be associated reliably with lesions to a particular area of the brain in both animal and human studies as well as functional imaging studies and those using electrophysiological recording it may be argued that it is reliably associated with function of a particular brain region. This does not resolve the problem that such studies rest on such assumptions but measures can be taken to provide evidence for the validity of such assumptions as much as possible. Furthermore, studies incorporating reliable controls improve the possibility of hypotheses being robustly tested against different interpretations of the findings.

Lines of converging evidence and evidence supporting the validity of relevant tasks are described in examination of one executive process which is the focus of this

investigation. That is active working memory, which can be described as the ability to hold information in mind, and manipulate that information in the short term. This may be linked to the ability to sustain attention to a task so as to take in ongoing relevant information that needs to be held in working memory. These abilities are important in everyday life, such as in complex tasks where information is held 'on line' so as to direct activity towards a particular goal.

Theories are beginning to emerge about the relationship between the dorsolateral prefrontal cortex (PFC) and aspects of working memory. Recent reviews of functional imaging studies (e.g. Caboza & Nyberg, 2000; Duncan & Owen, 2000) have implicated mid-dorsolateral, mid-ventrolateral and anterior cingulate areas as key regions in a range of higher-level tasks. These include working memory, attentional control, and inhibition of habitual or prepotent responses. The following section describes evidence linking the lateral PFC and active working memory.

1.2.1 Active monitoring and manipulation of information in working memory as a distinct function linked to the dorsolateral PFC

There is considerable evidence that the frontal cortex plays a critical role in certain aspects of working memory. This evidence comes from the study of patients with excisions to the prefrontal cortex (Owen, Downes, Sahakian, Polkey & Robbins, 1990; Owen, Sahakian, Semple, Polkey & Robbins, 1995; Petrides & Milner, 1982) and from lesion and electrophysiological recording work on nonhuman primates (Goldman-Rakic, 1987). For example, there is some evidence to suggest that damage to the dorso-lateral PFC (the dorsal part of areas 9 and 46) results in severe

impairment on self-ordered and externally ordered non-spatial working memory tasks (Petrides, 1991; 1995b) whilst other basic memory processing remains intact such as recognition memory. Thus, it is suggested that the dorsolateral PFC is implicated in tasks which require holding and manipulating information in working memory.

This function may be separable from other memory functions which require short term memory span but do not require active processing of information. In monkeys, lesions confined to Brodmann's area 46 of the dorsolateral prefrontal cortex result in severe impairments on tests of spatial working memory. For example, monkeys with dorsolateral frontal lesions perform well on delayed matching to sample tasks in which they have to recognise which one of two constantly recurring stimuli was most recently presented (Passingham, 1975) and on a delayed object alternation task in which they have to alternate their responses between two stimuli (Mishkin, Vest, Waxler & Rosvold, 1969; Petrides, 1995a). These tasks require mnemonic judgements based on the relative recency or primacy of stimuli. Such studies suggest that this kind of functioning need not be affected by dorsolateral frontal damage. Petrides has shown that for those with such damage memory only fails when the task becomes more challenging and requires self-ordered or externally ordered sequencing. Such tasks could be said to require remembering a number of stimuli which need to be actively monitored as responses are made. This monitoring function appears to be impaired in people with damage to the mid-dorsolateral area of the PFC (Petrides, 1995b).

Furthermore, evidence has accrued from PET studies with humans in which brain activation is measured while a person is performing a particular task. In a recent

review of PET and MRI studies, Caboza & Nyberg (2000) have demonstrated that tasks requiring sustained attention, or continuous monitoring of different kinds of stimuli, have consistently been linked to activation in the pre-frontal cortex. Several studies have demonstrated the role of the PFC in attentional modulation (e.g. Rees, Frackowiak & Frith, 1997), especially in tasks where the attentional load is high, and in working memory, which has been shown to be associated with increased activity in the PFC. This activity is typically found in areas 6, 44, 9 and 46, which are in the lateral PFC.

In these imaging studies, different patterns of activation have been shown to be associated with the performance of particular tasks. These studies are used to argue for dissociations between different executive functions and the areas which subserve them. For example, Petrides has proposed a model (Owen, 1997; Petrides, 1994, 1995b) suggesting that the mid-dorsolateral PFC (areas 46 and 9/46) is a specialised region for the on-line monitoring and manipulation of cognitive representations within working memory, as opposed to the ventrolateral PFC which is associated with active selection, comparison and judgement of stimuli held in short and long-term memory. He has argued that these represent two levels of executive control which are probably involved in several tasks and often simultaneously. In support of this model, studies have demonstrated activation in areas of the ventrolateral PFC but not in areas of the dorsolateral PFC on a spatial memory span task (Petrides, Alivisatos, Meyer & Evans, 1993b), and activation of the dorsolateral PFC but not the ventrolateral PFC in a non-spatial self-ordered memory task (Petrides et al., 1993a).

However, there are some limitations to the conclusions that can be drawn from such studies. For example, investigations have used a variety of tasks purported to tap working memory and have produced a variety of results which may suggest that such tasks may not be equivalent and may be tapping different functional deficits. For example, a distinction should be made between short term memory and working memory. Short term memory refers to temporary storage of information and short term memory problems are primarily associated with posterior cortical damage (Baddeley & Hitch, 1974). In contrast, working memory refers to a type of online processing of information which requires active monitoring and manipulation of information. This function may be processed quite differently from that of the storage component and there is evidence that simple short term spatial memory processes remain intact after dorsolateral PFC lesions (Diamond, 1990).

Most working memory studies have employed three types of tasks: delayed response, nback and self-ordered response. In each trial of delayed response tasks, subjects are presented with items which they are required to hold in short-term memory for a few seconds, and then make a response to a probe. The tasks generally require maintaining information in short-term memory. In the nback task (Rosvold, Mirksy, Sarason, Bransome & Beck, 1956), subjects must indicate whether or not each letter in a continuous stream of letters matches a letter that occurred one, two or more back in the series. This task involves not only short-term maintenance but also constant updating, which is an operation that is attributed to the central executive according to Baddeley's working memory model (Baddeley, 1986, 1998). This nback task has been shown to be particularly sensitive to processes of monitoring information in active working memory, which is associated with activation in areas 9 and 46, which

make up the mid-dorsolateral PFC (D'Esposito et al., 1998; D'Esposito & Postle, 1999).

Furthermore, the nback task can be used to measure speed of response as well as accuracy (Braver, Cohen & Servan-Schreiber, 1995). This is helpful in addressing the issue of the speed-accuracy trade-off in measuring performance on timed tasks. This refers to differences between individuals in how they choose to trade-off speed and accuracy in their patterns of performance, which can make understanding the performance of a group as a whole quite complicated. One way of making these issues clearer is to contrast performance on paced and unpaced versions of a task. In the unpaced version the participant tends to maintain accuracy by taking longer to respond, and in the paced version, the participant has much less time to respond so accuracy is more likely to be sacrificed.

As described earlier, there is evidence that executive aspects of working memory are selectively impaired in people with PKU, particularly on tasks tapping the dorsolateral PFC where neurons are considered to be especially sensitive to dopamine depletion. Thus, people with PKU are expected to show impaired performance in a task such as the nback described above. However, in order to understand the selectivity of executive impairments in PKU, one would need to contrast performance on a task such as the nback with performance in another area of executive functioning which is not thought to be so reliant on the dorsolateral PFC and its associated dopamine pathways. One cognitive model has recently suggested that there is a dissociation between monitoring of information in working memory, subserved by the dorsolateral PFC, and associative learning, subserved by the

orbitomedial PFC. The evidence for this dissociation is evaluated in the section below.

1.2.2 Dissociations between functions relying on the dorsolateral PFC and those relying on the orbitomedial PFC

Orbital and medial PFC regions have been linked to goal-oriented behaviour. In particular, these areas are thought to detect changes in reward-related information used to modify ongoing performance, including the guidance of social and emotional behaviour. Empirical studies using human and primate participants with brain lesions provide some support for a distinction between functions associated with the lateral PFC and those associated with orbital and medial areas (e.g. Bechara, Damasio, Tranel & Anderson, 1998; Dias, Robbins & Roberts, 1996a; Rolls, Hornak, Wade & McGrath, 1994). For example, strategic components of executive functions have been shown to be separate from online processing (Owen, Morris, Sahakian, Polkey & Robbins, 1996; Robbins, 1998). The evidence for this dissociation has mostly come from animal studies. For example, Dias, Robbins & Roberts (1996a) demonstrated a double dissociation between functions associated with lesions to the lateral PFC (area 9) and those associated with lesions to the orbitofrontal cortex (areas 11, 12 and 13). Furthermore, other recent studies have shown orbital lesions in monkeys are associated with impaired associative learning irrespective of working memory load (Bussey, Wise & Murray, 2001) and a dissociation was found between working memory and stimulus-response learning in rats (Galea et al., 2001).

Most recently, O'Reilly, Noelle, Braver & Cohen (2002) have put forward a computational model which proposes a dissociation between the orbitomedial PFC as the anatomical basis of associative learning aspects of executive functioning, and the dorsolateral PFC as the anatomical basis of active maintainance and monitoring of

information in working memory. Evidence has accrued which supports the hypothesis of dissociable neurochemical systems as well as anatomical systems in respect of the distinction made above, particularly in studies comparing the performance of patients with Alzheimer's disease (which is thought to be associated with the orbitofrontal system) and Parkinson's disease (which is thought to be associated with the dorsolateral system) (Freedman, 1990; Freedman & Oscar-Berman, 1986).

The task which appears to be most sensitive to intact functioning of the orbitomedial PFC is the Object Alternation task (Abbruzzese, Ferri & Scarone, 1997; Chorover & Cole, 1966; Curtis, Zald, Lee & Pardo, 2000; Freedman, 1990; Freedman, Black, Ebert & Binns, 1998; Freedman & Oscar-Berman, 1986; Gansler, Covall, McGrath & Oscar-Berman, 1996; Mishkin et al., 1969; Seidman et al., 1995; Zald, Curtis, Folley & Pardo, 2002). In this task, participants are presented with two objects and a reward (usually a coin) is hidden under one of the objects. Participants are required to try to make consistently correct responses, in which they choose the object under which the coin is hidden. Successful performance on this task requires the subject to learn a strategy or rule, such as that the coin alternates from one object to the other, or from one side to the other. Success is measured by the number of consecutively correct responses the subject makes.

There is also an element of delay in the task as there is a fixed period of time between presentations of the stimuli, requiring the subject to hold information in mind in the short-term. To date, this task has been administered manually. Preserved performance on this task has been shown to be associated with intact functioning of

the orbitomedial PFC in animal studies (Mishkin et al., 1969). This has also been found in human studies with samples of patients with brain lesions or neurological diseases, such as Parkinson's Disease (Chorover & Cole, 1966; Freedman, 1990; Freedman, Black, Ebert & Binns, 1998; Freedman & Oscar-Berman, 1986; Gansler, Covall, McGrath & Oscar-Berman, 1996), clinical disorders such as Obsessive-Compulsive Disorder and Schizophrenia (Abbruzzese, Ferri & Scarone, 1997; Seidman et al., 1995), and in PET studies (Curtis, Zald, Lee & Pardo, 2000; Zald, Curtis, Folley & Pardo, 2002).

Furthermore, functioning within the orbitofrontal cortex, on the basis of performance on similar alternation tasks, has been shown to be dissociable from functioning in tasks tapping the dorsolateral prefrontal cortex (Rolls, 2000). This is consistent with the hypothesis that the neurochemical effects observed in PKU may not lead to impaired functioning within the orbitomedial PFC, which has been shown to be less sensitive to fluctuations in dopaminergic neurotransmission (Rolls, 2000). Furthermore, stimulus-reinforcer association memory has been demonstrated to be distinct from the type of working memory implemented in the dorsolateral and inferior convexity prefrontal areas (Rolls, 2000; Rolls & Treves, 1998) which is supported by evidence that shows dissociations between performance on delayed response and inhibition tasks as opposed to alternation tasks which require associative learning (Bardenhagen & Bowden, 1998; Gansler et al., 1996). Thus, it may be argued that patients with PKU are unlikely to demonstrate impairments on an associative learning task, given the hypothesised specificity of cognitive deficits and their associated specific neurochemical and anatomical systems.

1.2.3 Dopaminergic lesions lead to more selective impairments than structural lesions

Dopamine is thought to play a central role in functions linked with the lateral PFC and associated pathways. However, primate evidence suggests that dopaminergic lesions may be associated with more selective impairment than structural lesions to the lateral PFC. For example, the removal of the dopaminergic input to the PFC in monkeys only disrupts performance on prefrontal tasks requiring active memory, but not those requiring inhibitory control (Collins, Roberts, Dias, Everitt & Robbins, 2000; Roberts et al., 1994). Detailed investigations of the differing processes contributing to performance revealed that dopaminergic lesions were associated specifically with reduced efficiency in processing higher working memory loads, but were not associated with reduced inhibitory control. This differed from the excitotoxic lesion group, where impairment was found both in active working memory and inhibitory control (Collins, Roberts, Dias, Everitt & Robbins, 1998). This suggests that dopaminergic lesions are associated with more selective deficits than structural lesions of the PFC.

There is also recent evidence to suggest that dopamine is important in the ability to make a delayed response, which is arguably reliant on holding information in working memory. For example, studies involving a neurochemical intervention have shown relationships between altered dopamine neurotransmission and poor performance on delayed response tasks (Aujla, & Beninger, 2001; Hironaka, Tanaka, Izaki, Hori & Nomura, 2001; Morrow, Roth & Elsworth, 2000; Sawaguchi & Iba, 2001). Neurons which receive dopaminergic inputs have been shown to be associated

with the ability to make delayed responses (Constantinidis, Francowicz, Goldman-Rakic, 2001; Diekamp, Kalt, Guentuerkuen, 2002; Druzin, Kurzina, Malinina & Kozlov, 2000; Floresco, Braaksma & Phillips, 1999; Murphy, 2001), and with the ability to manipulate and integrate information (Funahashi & Inoue, 2000). Furthermore, in studies measuring animals' patterns of brain activation, the dorsal anterior cingulate lesions (part of the noradrenergic system) has been implicated in behavioural sequencing (Delatour & Gisquet, 2001), and areas thought not to be involved in such dopaminergic pathways have been shown to be associated with normal performance on working memory tasks (Delatour & Gisquet, 2000). Only delayed response has been found to be impaired in primates with large dopamine and noradrenaline depletions (Roberts, Robbins, Everitt & Muir, 1992; Roberts et al., 1994). This suggests that there may be an association between dopaminergic functioning in the prefrontal cortex and working memory functions in particular.

However, there is very little evidence examining dopaminergic neurotransmission and task performance in humans. Extrapolating animal evidence to human cognitive models involves making assumptions about the comparability of human and animal brains and the relevance of the tasks given to animals for human performance. Nevertheless, studies are emerging in particular with relation to Schizophrenia and ADHD, as it has been suggested that altered dopaminergic systems may be implicated in some of the cognitive deficits observed in these conditions. For example, the activity of certain dopamine receptors have been shown to be related to selective impairments in people with Schizophrenia on a delayed response task (Goldman-Rakic, 1999). Also, there is some evidence linking Schizophrenia to an inherited disorder on the genotype that predicts prefrontal executive cognition and

working memory functioning (Cannon, van Erp, & Glahn, 2002; Weinberger, Egan, Bertolino & Callicott, 2002). Furthermore, an animal model of ADHD has been developed in which it is suggested that behavioural problems result from an imbalance between noradrenergic and dopaminergic systems in prefrontal cortex (Russell, 2002). However, the evidence in this area is only just beginning to accrue.

There is evidence to suggest that prefrontal dopamine systems have specific effects on working memory processes, but the relationship between working memory functions and dopaminergic systems within the PFC is complex. For example, low doses of dopamine receptor antagonists in the PFC have been suggested to lead to behavioural improvements (Williams & Goldman-Rakic, 1995), rather than deficits, whilst high levels of PFC dopamine activity are associated with poorer delayed performance in the rat (Murphy, Arnsten, Goldman-Rakic & Roth, 1996; Sahakian et al., 1985; Zahrt, Taylor, Matthew & Arnsten, 1997). These results suggest that the relationship between mesofrontal dopamine function and efficiency of working memory may be characterised by an inverted U-shaped function (Arnsten, 1998; Robbins, 1985; Zahrt et al., 1997), with dopaminergic activity also having been shown to have a modulatory role in attentional performance. However, Robbins (2000) has suggested that such modulation and its effects will depend many factors such as the nature of the task under study, as it has been shown that the effect of mesocortical dopamine depletion varies as a function of the task which is evident in impaired performance on a spatial delayed response task, unaffected performance in a spatial sequencing task, and improved performance on an extra-dimensional shift task, all of which are considered to tap executive components of working memory (Collins et al., 1998; Dias et al., 1996a; 1996b).

There is evidence for the impact of these factors on performance in the nback task. For example, Cohen & Servan-Schreiber (1997) demonstrated a distributed network of regions involved in nback performance with greater prefrontal activation as the working memory span demands of the task increased, yet loci within the dorsolateral PFC evinced exclusively an inverted-U shaped neurophysiological response from lowest to highest load, consistent with a capacity-constrained response. The results of this study were used to suggest that regionally specific nodes within the working memory network are capacity-constrained in the physiological domain, providing a missing link in current explorations of the capacity characteristic of working memory (Callicott et al., 1999). There is further evidence that working memory emerges from the formation of a dynamic cortical network linking task-specific processes with non-specific, capacity-limited, higher-order attentional processes (McEvoy, Smith & Gervins, 1998). Thus, there appear to be a number of processes involved in nback task performance, some of which are affected by working memory capacity and others which are not. It may be the case that the demonstrated activation in particular regions of the dorsolateral prefrontal cortex interacts with the modulatory effects of dopamine in such a way that there is not a straightforward relationship between dopamine depletion and deficits in capacity for processing information with a high working memory load.

1.2.4 Dopamine depletion and working memory impairments in PKU

The executive deficit hypothesis of PKU suggests that measures that place high demands on active working memory are likely to be sensitive to any impairments

mediated by dopamine depletion. Thus, given that depletion of dopamine in the dorsolateral PFC has been linked with both PKU and impairments in active working memory processes, we may expect people with untreated PKU to be relatively impaired in the efficiency with which they can process information with higher working memory loads. On the nback task mentioned above, this would be evident in their performance from a greater number of errors, and longer reaction times to stimuli than healthy control participants.

Thus, the dorsolateral PFC has been shown to be more sensitive to mild fluctuations in the level of dopamine than other parts of the PFC and the brain. The dorsolateral PFC and its associated dopaminergic neurotransmission systems have been shown to be associated with executive functions of monitoring information in working memory and attentional control. Thus, one might expect a task that has been shown to be associated with the dorsolateral PFC, such as the nback, to be sensitive to impairments mediated by dopamine depletion in adults with early and continuously-treated PKU, who have been off-diet since early adolescence. To test the selectivity of such executive impairments in PKU, performance would need to be contrasted with an alternative executive measure, reliant on dissociable systems within the PFC, in which functioning is expected to be preserved. The evidence reviewed above suggests that processes reliant on the orbitomedial PFC can be dissociated from those relying on the dorsolateral PFC. Reward-based learning has been shown to be dependent on intact functioning of the orbitomedial PFC and there is consistent evidence for the validity of the Object Alternation task as a test of this function.

1.3 MAIN FINDINGS AND LIMITATIONS OF EXISTING STUDIES

Research into the effect of dopamine depletion in PKU has so far demonstrated that starting treatment early and maintaining it well throughout childhood is likely to lead to better outcomes in terms of comparable levels of IQ, compared with healthy controls and unaffected family members. Furthermore, research has suggested that, notwithstanding such treatment with a well-controlled diet, children display selective executive deficits in the efficiency with which they can process information with a high working memory load. It has been hypothesised that this is due to the effects of dopamine depletion on the dorsolateral prefrontal cortex, where neurons are especially sensitive to mild fluctuations in dopamine, compared to other areas of the brain. This is consistent with evidence from localisation studies which have shown an association between the dorsolateral prefrontal cortex and performance in tasks requiring processes of active working memory.

Attempts to test the selective executive deficits hypothesis in PKU have mostly been in studies with children. Here the findings have been mixed. For example, Griffiths et al. (1998b) found that the early and continuously treated children with PKU did not show any impairment on either the one-back or two-back versions of the task in comparison to healthy controls. This concurs with the findings of Mazzocco et al. (1994) and Stemerdink et al. (1994) who found no significant executive function deficits in school-age children with treated PKU. However, other studies have demonstrated selective deficits in children with PKU on tasks sensitive to executive processes of working memory, attention and speed of information processing

(Diamond et al., 1997; Weglage et al., 1996; Welsh et al., 1990; Welsh & Pennington, 2000).

There are a number of possible explanations for these mixed findings. One difficulty interpreting the differences across studies is caused by the use of different measures sensitive to executive functions. It is therefore uncertain whether the differences in findings are due to task differences. Measurement issues become particularly complicated when working with children because there are no executive tasks that have been neurologically validated, such as where selective deficits have been demonstrated in children with known frontal-lobe dysfunction. In many instances, tasks are purported to be measures of frontal-lobe function because their demands are similar to the demands of the tasks used with adults who have frontal-lobe lesions (Smith, Kates & Vriezen, 1992). For example, Stemerdink et al. (1994) used tasks sensitive to information processing deficits; however, it is unclear to what extent these tasks had an executive component, as the authors recognise "the tasks used made only a small demand on higher-order cognitive processes" (p.107).

In contrast, Diamond (Diamond, 1994; Diamond et al., 1997) chose a very different set of tasks, developed not only from the literature on the effects of frontal-lobe lesions on human adults but also from the literature based on animal studies. In Diamond's studies two groups of measures were used. One was developed from measures shown empirically in studies of adults or monkeys to be dependent on the prefrontal cortex, and the other to be dependent on parietal or temporal cortex. Deficits were observed in the former only, thus being specific to the prefrontal system. Furthermore, Ris et al. (1994) used the Attention Diagnostic Method which

is an experimental test which the authors argue has been shown to be sensitive to information processing deficits in PKU (Berry, Brunner, Hunt & White, 1990). These authors also found significant group differences between a PKU and a control group in reaction times on this measure.

However, these studies have used a variety of different cognitive measures. To examine the hypothesised selectivity of executive deficits in PKU careful choice of tasks is necessary, including the use of control tasks which appear to be sensitive to different executive processes. In the literature on PKU so far, some studies have used tasks supported by the human and primate lesion and imaging evidence and some have not. It is therefore argued that the selective executive deficit hypothesis in PKU has not yet been robustly tested. Also, many studies have used small sample sizes which may have reduced the statistical power of analyses. Furthermore, there are very few published studies which have attempted to test the hypothesis in adults with PKU, who have been treated early and continuously throughout childhood, but who have been exposed to higher than normal Phe levels in adulthood. Thus, there is presently scant knowledge about the effects of exposure to elevated Phe concentrations on executive skills, particularly in adolescence and beyond (Griffiths, Campbell & Robinson, 1998; Zetterstrom, 1995).

Thus, the selective executive deficit hypothesis has not been tested in adults with PKU. Such information would be highly relevant to clinicians working with such patients, who presently have little evidence on which to base decisions as to whether or not to return to diet. As many have previously been advised to come off diet, the decision to return would involve a major lifestyle change and a high level of

commitment to treatment. If the evidence were to support such executive deficits in untreated adults, the level of motivation to return to treatment may be higher.

In addition, present studies in the field of PKU research have used a wide variety of measures, with insufficient controls built into the designs, and using small sample sizes. This hampers reliable evaluation of what cognitive functions each task is tapping, how these may be relevant to selective dopamine depletion, and the extent to which the studies have controlled for confounding variables. An ideal design for testing the selective executive hypothesis of PKU would be to carry out a randomised controlled trial, with the performance of on and off diet groups measured longtitudinally with tasks supported by the evidence from localisation studies. However, this would not be possible for ethical reasons.

An alternative method of testing the hypothesis would be to compare a group of adults with PKU with healthy controls, in their performance on a task reliably shown to tap active working memory. Such performance would be compared on a control task which taps another element of executive functioning, but which is though to be less reliant on dopamine neurotransmission. On the basis of evidence of dissociations within the prefrontal cortex. a task tapping a function thought to be associated with the orbitomedial prefrontal cortex, such as the Object Alternation task, may be a suitable executive function control task.

Given that the deficits in those with PKU are argued to be selective to executive functions it would also be necessary to control for performance on a non-executive task, in which performance does not rely heavily on executive functions. In such a

task performance would be expected to be comparable between patient and control groups. The reason for including such a task in the design would be to control for the possibility that the particular population sampled in the study were impaired in other non-executive areas of functioning. If the group with PKU perform worse that the control participants on both measures of executive functioning, and there is no non-executive control measure, it would be impossible to say that the study disproved the selective executive deficit hypothesis. Other explanations of such findings could be that the population with PKU sampled showed generalised cognitive deficits not specific to executive functions, or that there were other non-executive difficulties that mediated performance on the two executive tasks. Thus, if the study was designed using the two measures alone it would not be possible to prove or disprove the hypothesised selective executive deficit in people with PKU.

It may not be practically possible to test those with PKU on every other type of non-executive cognitive function. Also, identifiying tasks that do not draw on the PFC is problematic, since PET and fMRI studies have demonstrated that areas of hte PFC are activated to some extent in almost all high-level tasks. Nevertheless, tasks thought to draw predominantly on posterior brain regions, such as relatively simple perceptual judgements appear to make fewer demands on the PFC than tasks such as those described above (e.g. Caboza and Nyberg, 2000). Lesion studies have shown impairments in patients with posterior lesions on tasks including the matching of objects according to physical shape (associated with right posterior regions), and matching according to object function (associated with left posterior regions) (De Renzi et al., 1969). Thus in the present study, participants will be asked to make simple forced-choice perceptual judgements of object shape and function matching,

taken from the Birmingham Object Recognition Battery (Riddoch & Humphreys, 1993) which has been shown to be associated with activation of such posterior regions (Humphreys & Riddoch, 1993). It is predicted that participants with PKU will perform at similar levels to healthy control participants on these tasks.

Even with this added control measure another difficulty with this design is that other difficulties on the part of the PKU participants, perhaps linked to the social and emotional difficulties associated with this life-long disorder, could account for differences in performance between the two groups. For example, it may be argued that the presence of mental health problems, dysexecutive symptoms impacting on everyday life, or a generally poorer quality of life could account for such differences. Thus, it would be important to attempt to measure such variables so as to have some indication of whether such problems could account for performance in the cognitive tasks. There are several ways of capturing such problems, but for the sake of brevity in the period of time of each participant's assessment, short but robust questionnaire measures were used in the current study. Reasonably valid and reliable measures of such difficulties in everyday life were used. These are The Beck Depression and Anxiety Inventories for measuring of symptoms of depression and anxiety, the SF-36 as a measure of general quality of life within domains of both physical and mental health, and the DEX questionnaire as a measure of dysexecutive symptoms. Due the lack of awareness of the extent of their difficulties in some people with executive problems the DEX questionnaire is given to both the participant and, with their consent, an informant who knows them well.

Finally, many of the studies described above have attempted to correlate task performance with concurrent blood Phe levels at the time of testing, under the assumption that the higher the blood Phe levels, the greater the depletion of dopamine in the brain, and thus the greater the extent of impairments on cognitive tasks. Some studies have demonstrated such a relationship (Diamond et al., 1997; Pietz et al., 1998; Ris et al., 1994; Smith et al., 1996; Weglage et al., 1996; Welsh et al., 1990), but others have not (Griffiths, Campbell & Robinson, 1998; Griffiths, Tarrini & Robinson, 1997). The equivocal findings may be due in part to differences in tasks and designs as suggested above, but also to the fact that blood Phe levels are only an indirect measure of brain Phe levels (see e.g. Koch et al., 2000).

It may also be helpful to measure concurrent blood Phe levels of the PKU group against performance on the working memory task, as this is the most reliable indicator available of the patients' levels of brain Phe, and hence extent of dopamine depletion in the brain. The control group would have to be matched with the PKU group on age, IQ and educational background so as to control for the impact of levels of IQ and experience on performance on the tasks. Furthermore, those participants with other neurological and psychological problems would have to be excluded from the analysis so as to control for the effects of these confounding variables on performance in the tasks.

1.4 AIMS OF PRESENT STUDY AND HYPOTHESES

PKU has been linked exclusively to impairments in tasks linked to dopamine depletion in the dorso-lateral pre-frontal cortex. In the sections above it has been suggested that performance in tasks that require reward-based learning can be

dissociated from performance on tasks that require processing higher working memory loads as the memory demands of these different types of tasks are thought to be mediated differently within the brain. The processing of high working memory loads has been shown to be linked to dopamine depletion in the dorsolateral prefrontal cortex, and the use of reward-based learning to guide ongoing behaviour has been linked to the orbitomedial prefrontal cortex, which is less reliant on dopamine neurotransmission. Thus, one may expect a difference in performance in tasks tapping these two functions in people who have been shown to have selective dopamine depletion, which is purported to impair functioning within the dorsolateral prefrontal cortex.

As people with PKU have been shown to have such selective dopamine depletion, one would expect them to perform as well as controls on the reward-based learning task, but to be impaired compared to controls on the processing of high working memory loads. This is the key hypothesis which is tested in the current study. One would expect people with PKU who are currently untreated to be selectively impaired in their performance on tasks sensitive to efficiency in processing higher working memory loads, such as the n-back task, but not on tasks sensitive to reward-based learning, such as the Object Alternation task.

1.4.1 Hypotheses

1. Adults with treatment-discontinued PKU, who have been early and continuously treated throughout childhood, will be significantly impaired in the efficiency with

which they can process higher working memory loads in comparison to matched controls from the normal population.

2. Those with PKU will not show significant impairments in a task tapping another executive function of reward-based learning, which is thought to be less reliant on the dorsolateral prefrontal cortex, compared to healthy control participants.
3. The patient and control groups will perform comparatively on a task which places minimal demands on executive functions.
4. Performance on the active working memory task will be negatively correlated with concurrent blood Phe levels of the patient group.

2.0 METHOD

2.1 Design

A between-subjects design was used to compare 20 adults with PKU to 20 healthy adult control participants.

2.2 Participants

The PKU and control groups were matched for sex, age, IQ, and years of education.

2.2.1 PKU group

The PKU group were recruited via a national service for people with metabolic disorders. The Consultant in Metabolic Medicine and the Dietician at the Metabolic Unit were involved in selection of participants for the study. Selection was based on the criteria described below. As there was only a small pool of potential participants all those fitting the criteria within the service were considered and contacted if appropriate. The Consultant wrote to potential participants providing information about the study and inviting them to be contacted by the researcher should they be interested in finding out more. Those who agreed to be contacted were telephoned by the researcher and there followed a discussion of the purposes of the study in brief and what it would involve. If the person was interested in being involved an appointment was made over the telephone and confirmed in writing.

To be included in the study, participants had to have a diagnosis of PKU, having been diagnosed and started on treatment within the first month of life. The treatment consists of a restricted intake of natural protein and supplementation of the diet with amino acids, vitamins and minerals. This diet is the standard treatment for people with PKU. Before 1991 patients attending the clinic at the Metabolic Unit were advised to come off the diet during late childhood or adolescence. Those with PKU included in the present study had come off the diet in accordance with medical advice and had been continuously treated up to this point.

As it is not possible to measure the level of neurotransmitters directly, the main way of estimating the extent to which dopamine neurotransmission is affected in those with PKU is by measuring the level of Phenylalanine (Phe) in the blood. The acceptable level in a normal population is up to 700 μmol/L but as those sampled in the present study are untreated they are likely to have a much higher level of blood Phe. The general principle is that the higher the levels of blood Phe, the greater the extent of dopamine depletion in the brain.

Participants with other neurological problems, current mental health problems, alcohol or drug dependence, diagnosed physical conditions which interfere with fine motor movement, or where English was not their first language were excluded from the study.

2.2.2 Control group

The control group consisted of healthy adult volunteers who were matched to the PKU group on gender, age, years of education and IQ. IQ was estimated using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). A description of the WASI is given in the section below.

The same exclusion criteria as applied to the PKU group also applied to the selection of participants for the control group.

2.2.3 Sample characteristics

Matching between groups

As Table 1 indicates, there were no significant differences between groups in terms of age, IQ and years of education. Both groups contained 13 (65%) men and 7 (35%) women.

Table 1:Matching between groups

	PKU N = 20		**Control N = 20**			
Group	**M**	**(SD)**	**M**	**(SD)**	**Test**	**Sig.**
Gender	13m, 7f		13m, 7f			
Age (years)	28.35	4.23	31.00	7.30	t=1.41	NS
WASI Full Scale IQ	102.55	14.42	106.70	8.69	t=1.10	NS
Years of education	12.85	2.16	12.65	1.42	t=0.35	NS

2.2.4 Characteristics of the PKU group

Each participant's concurrent blood plasma (Phe) levels were measured by a blood sample taken on the day of testing and the participants were asked about when they had come off the diet. These are summarised in the table below for the participants sampled in the present study.

Table 2:Age diet discontinued and concurrent Phe levels of PKU group

	Age stopped diet	Mean conc. Phe level (μmol/L)
N	20	20
Mean	14.60	1264.60
S.D.	2.50	183.99
Variance	6.25	33853.31
Range	9-18	990.00-1651.00

2.3 Procedure

The Joint University College London and University College London Hospital's Committee on the Ethics of Human Research gave ethical approval to Dr Channon. The present study was subsumed within a wider project, which has been given approval under the supervision of Dr Channon. Copies of the approval notices, information sheet and consent forms are provided in the Appendices.

At the start of each session participants were given time to read the information sheet and ask questions about the procedure. If agreeable, each participant was then asked to provide written consent.

A counterbalanced order of administration for the tests was used to ensure that any effects of fatigue or practice were similar for all the participants. Each condition of

the nback and the two perceptual tasks were considered as separate tests and the computer tests were also interpsersed with WASI sub-tests so that the participants did not have to spend an extended amount of time looking at the computer screen. Breaks between tests were provided as necessary to help minimise the effects of fatigue and for the participants' comfort.

Each participant's travel and subsistence expenses were paid to cover time and effort expended in participating in the study.

2.4 Measures

2.4.1 Screening measures

Health Screen Interview

This is a specially designed questionnaire to obtain information about educational and occupational history, psychiatric and drug and alcohol history, and medical and neurological history. A copy is provided in the Appendix section.

Beck Depression Inventory - version II (BDI-II) (Beck,1996)

The BDI is a self-report measure of symptoms of depression, which has been validated against psychiatrist evaluations. Ratings are attained as to whether or not the person's ratings fall within the clinical range for depression. It has been successfully validated against psychiatrist evaluations, but has been shown to have poor specificity. Nevertheless, it has been shown to have a high degree of internal

consistency with a Chronbach's alpha correlation co-efficient of .92 and a test-retest reliability co-efficient of .93 (Beck et al., 1996).

Beck Anxiety Inventory (BAI) (Beck, 1990)

The BAI is a self-report measure of symptoms of anxiety, which has been validated against psychiatrist evaluations. Ratings are attained as to whether or not the person's ratings fall within the clinical range for anxiety. It has been successfully validated against psychiatrist evaluations, and has been shown to have an acceptable level of sensitivity and specificity. It has also shown to have good internal consistency with a alpha correlation co-efficient of .94 (Fydrich et al., 1990) and reasonable test-retest reliability with correlation co-efficient of .75 ($p<0.001$) (Beck, Rush, Shaw & Emery, 1979).

Quality of life questionnaire – SF-36 (version 2) (Jenkinson, Stewart-Brown, Petersen & Paice, 1999)

The UK version of the SF-36 was used as a self-report measure of quality of life. It was developed for the Medical Outcomes Study and has been tested and validated extensively. It is a 36-item questionnaire that measures health status in eight domains of mental and physical health. These are physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, energy/vitality, pain and general health perception. For the purposes of the current study the Physical Component and Mental Component Summary Scores were calculated because these were suggested in the manual to be good indices of general physical and mental health. The domains of functioning within this measure

have been shown to have good internal consistency ranging from co-efficients between 0.80 and 0.95 (Jenkinson, Stewart-Brown, Petersen & Paice, 1999).

DEX (Dysexecutive questionnaire from the BADS battery): self-report and informant (Wilson, Alderman, Burgess, Emslie & Evans, 1996)

This is a 20-item Dysexecutive Questionnaire (DEX). The items are constructed in order to sample the range of problems that are commonly associated with Dysexecutive Syndrome in four broad areas: personality, motivation, behavioural and cognitive domains. Each item on the DEX is rated on a five-point scale of problem severity. The DEX comes in two forms. One is designed to be completed by the person and one is designed to be completed by an informant such as a family member. As stated in the Introduction section, this accounts for the possibility that the person with symptoms of executive problems has reduced insight into the extent of their difficulties as shown by significant self and other-reported discrepancies in clinical populations ($t=2.85$, $p=.006$) (Wilson, Alderman, Burgess, Emslie & Evans, 1996).

2.4.2 Neuropsychological measures

General intellectual functioning

Wechsler Abbreviated Scale of Intelligence (WASI), (Wechsler, 1999)

The WASI is designed to provide a short method of estimating intellectual function, and it is linked to the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Wechsler, 1997). It comprises four sub-tests of the WAIS III; Vocabulary, Block Design, Similarities and Matrix Reasoning. Scores on both the Vocabulary and Similarities sub-tests are used to estimate Verbal IQ (VIQ), which is a measure of various abilities including verbal reasoning and comprehension. Scores on both the Block Design and Matrix Reasoning subtests are used to estimate Performance IQ (PIQ). Taken together, these four sub-tests provide the Full Scale IQ (FSIQ) score, which is an estimate of general intellectual ability. These four sub-tests were chosen, in particular, because they have the highest loading on general intellectual functioning of all the sub-tests of the WAIS-III. This is supported by validity studies demonstrating that WASI FSIQ scores account for 85% of the variance in WAIS-III FSIQ scores (Wechsler, 1999). In addition, Wechsler (1999) reports internal consistency and reliability co-efficients of 0.96 for VIQ, 0.96 for PIQ and 0.98 for FSIQ.

Attention and working memory

N-back

The nback task is a delayed response measure that has been widely used in the experimental working memory literature (e.g. Braver, Cohen & Servan-Schreiber, 1995). In this task, participants are presented with a series of letters, and respond to each with the dominant hand, pressing one button for targets and another for non-targets. The effects of varying memory load are examined by comparing performance in 3 conditions; (i) 0-back (respond to the present letter), (ii) the 1-back (compare present letter with the preceding one), and (iii) the 2-back (compare with letter presented two trials back) conditions. In each condition, 50% of trials are targets and 50% are non-targets. For all conditions the inter-trial interval was set at 1.2 seconds, and stimuli duration at 0.3 seconds. Reaction times and responses made are recorded by the specially-designed computer programme.

Unpaced nback task

In the unpaced nback task a new trial is presented only once the participant has responded to the stimulus. Thus, this allows the participant to set the pace of their responses.

Paced nback task

In the paced nback task each trial is only presented for 0.3 seconds with an inter-trial interval of 0.3 seconds. This forces the participants to respond faster to keep up with the speed of presentation of trials.

Reward-based learning

Object Alternation

In this task the participant is shown two objects, hidden underneath one of which is the reward, a coin. The participant chooses one object on each trial and is told to try and find the coin every time. Having made a choice, the participant is shown whether the coin is or is not actually hidden under the object they chose. Thus, the participant has to try to determine the correct strategy for finding the coin, based on their learning of when their choices are right and wrong. Between each trial there is a fixed delay period before they can choose again. In the present study, this task was presented on computer, in contrast to the manual presentation used in the published literature. There is no evidence of use of a computerised version of this task in the published literature. However, for the purposes of this study such a version was used so as to allow accurate measure of reaction times to each of the trials. In accordance with the usual administration of this test, the inter-trial interval was set at 5 seconds, and the stimulus duration at 1 second. This computerised version was piloted on six members of the university department so as to ensure that the task on computer appeared to be generally easy to use and that the presentation of the task was clear.

Visuo-perceptual skills

Birmingham Object Recognition Battery (BORB) (Riddoch & Humphreys, 1993)

Two sub-tests: Association Match and Minimial View Match

As described in the Introduction, two sub-tests were selected from this battery which were measures of ability to make forced-choice perceptual judgements of object shape and function matching. For ease of measuring reaction time and response, stimuli pictures were scanned into a computer and were presented on the monitor screen. In these sub-tests participants are asked to make simple forced-choice perceptual judgements. In both of the tasks participants are presented with a stimulus picture and then two new pictures at the bottom of the screen, one of which is the target and the other which is the distractor. In the Association Match task, participants are required to choose which of the target pictures is associated with the stimulus picture (e.g. a letter is associated with an envelope). In the Minimal View task, participants are required to choose which of the target pictures is the same as the stimulus picture, but shown from a different perspective. Participants use their dominant hand to press left and right buttons. These two computerised tasks were also piloted on six members of the university department for ease of use and clarity of presentation.

3.0 RESULTS

3.1 Normality of distribution of the data

In general, non-parametric tests were used whenever the data did not satisfy the assumptions underlying parametric tests. Because skewness of distribution and outliers might violate the assumptions of normality and linearity underlying the parametric tests, the data were inspected for these. The degree of skewness was calculated for each variable, and compared against the standard error for skewness using the formula given by Tabachnick and Fidell (1983), to see whether it differed significantly from zero:

The standard error for skewness is

$$Ss = v6/N = v6/20 = 0.3$$

Where N is the number of cases. The probability of obtaining a skewness value of this size is

$$z = \frac{S - 0}{Ss}$$

Where S is the value for skewness. At the 1% level, a z value in excess of +/_ 2.58 would lead to rejection of the assumption of normality.

Entering this into the equation,

$$S = +/- 2.58 \times Ss = +/- 2.58 \times 0.3 = +/- 0.774$$

A criterion of +/- 0.774 was therefore used for the present data as a cut-off point for normality.

The data were also checked for outliers, using a standardised score of +/- 3.00 (or 3 standard deviations from the mean) as the cut-off point for continuous variables (Tabachnick & Fidell, 1983). Standardised scores were calculated for each variable, to identify which contained any values outside these limits.

To reduce the skewness of data to an acceptable degree and deal with the outliers, logarithmic transformation was used for reaction time data on the Alternation task, and negative reciprocal transformation was used for reaction time data on the nback task, thus parametric tests were performed on the log scores for these variables. Where data was transformed, raw means and standard deviations are reported. Transformation did not improve the normality of distribution of accuracy data on the nback task, which was highly positively skewed, but extent of outliers on this data was very limited, so, in the absence of non-parametric tests for repeated measures comparisons, parametric tests were used.

3.2 Demographic profiles of the two groups

The demographic profile of the two groups of PKU participants and healthy control participants were compared on dimensions of age, gender, Full-Scale IQ (on the basis of the WASI), level and years of education. A summary of these dimensions for the two groups are presented in the Method section.

On each of the variables of age, Full Scale IQ (on the basis of the WASI), years and level of education, the groups' means were compared with independent samples t-tests. The groups did not differ significantly on mean age ($t(38)=1.41$, $p=.170$), Full Scale IQ ($t(38)=1.10$, $p=.277$), mean years of education ($t(38)=.346$, $p=.732$). Thus, the two groups were considered to be well-matched and none of these factors were considered as confounding variables in the following statistical analyses.

Table 3: Summary of self-reported mental health and quality of life data

	PKU		Control			
Group	**M**	**(SD)**	**M**	**(SD)**	**Test**	**Sig.**
BDI Score[*a]	3.35	3.80	4.28	6.08	t=0.57	NS
BAI Score[*b]	3.35	3.73	3.16	5.04	t=0.14	NS
SF Phys.Comp. Summary Score[*c]	54.16	5.67	55.19	4.55	t=0.59	NS
SF Ment.Comp. Summary Score[*c]	52.44	8.52	52.08	9.18	t=0.12	NS
DEX self-rated[*d]	11.95	7.05	12.50	8.69	t=0.22	NS
DEX ind.-rated[*e]	13.89	9.48	9.73	7.85	t=1.22	NS

[*a] PKU group(n=20),Control group(n=18), [*b] PKU group(n=20),Control group(n=19)
[*c] PKU group(n=20),Control group(n=16) [*d] PKU group(n=20),Control group(n=18)
[*e] PKU group(n=18), Control group(n=11)

Unfortunately, some participants chose to complete the questionnaires at home and some were not returned therefore some of the data are missing. As all the measures

fulfilled tests of normality of distribution, t-tests were used to examine differences in mean scores between the two groups.

On each of the self-report measures; the Beck Depression Inventory (BDI) (Beck, 1996), the Beck Anxiety Inventory (BAI) (Beck et al., 1990), and the SF-36 Quality of Life Questionnaire (SF-36) (Jenkinson et al., 1999), the groups' means were compared with independent samples t-tests. The groups did not differ significantly on mean BDI scores ($t(36)=.57$, $p=.572$), or BAI scores ($t(37)=.14$, $p=.893$). The groups did not differ significantly on the SF-36 mean Physical Component Summary Scores ($t(34)=.59$, $p=.558$) or the mean Mental Component Summary Scores ($t(34)=.12$, $p=.904$). Finally, the two groups did not differ significantly on either the self-reported questionnaire of dysexecutive symptoms (DEX) ($t(36)=.22$, $p=.831$), or the similar independent-rated questionnaire ($t(36)=1.22$, $p=.233$). Thus, the two groups were considered to be well-matched in terms of mental health and quality of life so these factors were not considered as confounding variables in the following statistical analyses.

In the following sections, analyses are reported according to each hypothesis, and thus, each task. For each task both speed and accuracy were taken into account in the analyses. Reaction times are given in seconds for clarity of presentation.

3.3 Performance on the unpaced working memory task

To test hypothesis one, the groups' performance on the working memory task, the n back, were compared. Two key indicators of participants' performance on the tasks were calculated for comparison between groups. These were the mean of correct responses in total, and mean reaction times to correct trials.

Table 4:Mean correct responses on unpaced nback task

	PKU N = 20		Control N = 20	
Group	**M**	**(SD)**	**M**	**(SD)**
0-back	155.25	4.32	156.90	2.51
1-back	153.30	5.16	154.20	6.08
2-back	134.75	10.95	135.70	9.94

The table below shows results of multivariate analysis of variance tests on the two groups' accuracy data, using Pillai's Trace. Group's performance was compared across the 3 conditions of the nback task.

Table 5: ANOVA analysis of accuracy on the unpaced nback task

Effects	**F**	**Df**	**P**	**Sig. (2-tailed)**
Task	53.82	1,38	.0001	Sig.
Group	0.473	1,38	.496	NS
Task x Group	0.097	1,38	.908	NS

The analysis of variance revealed a main effect of task, with all groups performing less accurately as the attentional demands of the task increased.

Table 6: Reaction times to correct trials on the unpaced nback task

	PKU N = 20		Control N = 20	
Group	**M**	**(SD)**	**M**	**(SD)**
0-back	0.43	0.05	0.39	0.04
1-back	0.59	0.16	0.54	0.12
2-back	1.45	1.23	1.12	0.64

The table below shows results of multivariate analysis of variance tests on the two groups' reaction time data, using Pillai's Trace. Group's performance was compared across the 3 conditions of the nback task.

Table 7: ANOVA analysis of reaction times on the unpaced nback task

Effects	**F**	**Df**	**P**	**Sig. (2-tailed)**
Task	222.53	1,38	.0001	Sig.
Group	4.227	1,38	.047	Sig.
Task x Group	1.22	1,38	.306	NS

The analysis of variance revealed main effects of both task and group. Both groups had longer reaction times as the attentional demands of the task increased (from 0-back to 1-back, and 1-back to 2-back) and the PKU group had longer reaction times than the control group across conditions of the task.

3.4 Performance on the paced working memory task

The groups' performance on the paced working memory task were also compared with regards to accuracy and speed of responding. Because reaction time data were negatively skewed, negative reciprocal transformation was performed on the data but the raw means and standard deviations are presented below.

Table 8: Mean correct responses on paced nback task

	PKU N = 20		Control N = 20	
Group	**M**	**(SD)**	**M**	**(SD)**
0-back	74.20	5.21	76.35	3.25
1-back	71.55	6.19	73.10	5.87
2-back	55.65	10.95	63.00	9.94

The table below shows results of multivariate analysis of variance tests on the two groups' accuracy data, using Pillai's Trace. Group's performance was compared in all 3 conditions of the nback task.

Table 9: ANOVA analysis of accuracy on the paced nback task

Effects	F	Df	P	Sig. (2-tailed)
Task	47.96	1,38	.0001	Sig.
Group	4.32	1,38	.045	Sig.
Task x Group	2.34	1,38	.111	NS

On the paced task, there were main effects of both task, in a similar direction to the above, and of group, with the PKU group performing less accurately than the Control group. There was no interaction effect between task and group in the accuracy of responses on the paced working memory task.

Table 10: Reaction times to correct trials on the paced nback task

Group	PKU N = 20		Control N = 20	
Group	**M**	**(SD)**	**M**	**(SD)**
0-back	0.37	0.09	0.35	0.04
1-back	0.45	0.11	0.39	0.08
2-back	0.51	0.18	0.47	0.16

The table below shows results of multivariate analysis of variance tests on the two groups' reaction time data, using Pillai's Trace. Group's performance was compared in all 3 conditions of the nback task.

Table 11: ANOVA analysis of reaction times on the paced nback task

Effects	F	df	P	Sig. (2-tailed)
Task	30.52	1,38	.0001	Sig.
Group	1.65	1,38	.207	NS
Task x Group	1.22	1,38	.306	NS

On the paced task, there was a main effect of task, as all participants had longer reaction times as the attentional demands of the task increased. There was no interaction effect between task and group on the paced working memory task.

In summary, significant group effects were found in the accuracy data on paced trials, with the PKU group performing less accurately than the Control group. Furthermore, significant group effects were also found in the speed data on the unpaced trials, with the PKU group performing more slowly than the Control group.

3.5 Comparing group performance on the reward-based learning task

To test hypothesis two, the two groups' performance on the reward-based learning task, the alternation task, were compared. In the alternation task, three indicators of performance were calculated. These indicators are (i) the number of correct choices (i.e. finding the coin), (ii) the number of people who achieved 5 consecutive correct trials (as an indicator that the person may be responding with a correct strategy), and (iii) the median reaction time (RT) for correct choices. Because the reaction time data were skewed, these data were transformed. However, the raw means and standard deviations are presented below.

Table 12: Analyses of speed and accuracy performance on the alternation task

Group	PKU N = 20		Control N = 20		Test	2-tailed Sig.
	M	(SD)	M	(SD)		
Mean correct trials	30.80	9.68	31.05	7.37	t=0.09	NS
Mean RT correct trials	0.91	0.53	0.88	0.51	t=0.40	NS
% achieved 5 consecutive correct	65%	80%			?²=1.1	NS

As can be seen from the tables above, the groups did not show significantly different performance on any of the performance indicators on the reward-based learning task.

3.6 Comparing group performance on the perceptual task

To test hypothesis three, the two groups' performance on each condition of the perceptual task were compared. The two conditions were a shape matching task, and an association match task. The two indicators of performance used on these tasks were number of correct responses and median reaction time (RT) to trials where correct responses were made. The means of each of these indicators for each task are presented below, separated by group.

Table 13: Comparison of speed and accuracy performance on the perceptual tasks

Group	PKU N = 20		Control N = 20		Test	2-tailed Sig.
	M	(SD)	M	(SD)		
Correct trials on shape	19.80	0.41	19.75	0.72	z=0.33	NS
Correct trials on assoc.	19.35	1.01	19.60	0.60	z=0.35	NS
Correct RT on shape	0.86	0.20	0.80	0.30	t=1.09	NS
Correct RT on assoc.	0.97	0.24	0.94	0.29	t=0.59	NS

As transformation was not sufficient to reduce skewness of the data to an acceptable level (as both groups performed highly accurately on the task), non-parametric tests were used. The Mann-Whitney test used to compare the accuracy of the two groups' performance in this task suggested no significant differences in performance between the PKU and control groups. Independent samples t-test used to compare reaction times of the two groups to the correct trials on the perceptual tasks also showed no significant differences between the speed of responding of the two groups. The interpretation of these analyses was substantively similar on the basis of parametric tests which were carried out for comparison.

3.7 Correlating performance on the tasks with Phe levels in the PKU group

In order to test hypothesis 4, performance on each of the tasks was correlated with concurrent Phe levels of the PKU group, which are tests of the level of blood Phenylalanine on the day of testing, expressed in μmol/L.

The relationship between task performance on the nback task and concurrent Phe levels were considered. To reduce the number of comparison only six measures of task performance were considered; speed on the three conditions of the unpaced task, and accuracy on the three conditions of the paced task. On the unpaced task, concurrent Phe levels were not significantly correlated with reaction times to the 1-back (r=.397, p=.083) or the 2-back (r=.091, p=.703). However, there was a significant positive correlation between concurrent Phe levels and unpaced 0-back reaction times at the 0.01 level (r=.57, p=.009, Sig. 2-tailed). Taking a cautionary approach the probability level was divided by the number of comparisons made and with this approach the correlation no longer reaches significance. On the paced task, concurrent Phe levels were not significantly correlated with accuracy on the 0-back (r=.170, p=.475), 1-back (r=.372, p=.106) or the 2-back (r=.351, p=.129) conditions.

The age that the PKU participants stopped diet was also compared with the indices of task performance on the n-back. Age of discontinuation of diet was not significantly correlated with reaction times on the unpaced task on the 2-back condition (r=.069, p=.771) but it was positively correlated with unpaced 0-back reaction times (r=.48, p=.034, Sig. 2-tailed) and unpaced 1-back reaction times (r=.45, p=.049, Sig. 2-tailed). However, these significant results may be an artefact as they no longer reach

significance when divided by the number of correlations computed.There were no significant correlations between age of discontinuation and accuracy scores on the 0-back (r=.276, p=.238), 1-back (r=.359, p=.120) or 2-back (r=.328, p=.158) conditions.

Finally, it is interesting to note that the age that the PKU participants came off the dietary treatment was positively correlated with their concurrent blood Phe level (r=.50, p=.034, Sig. 2-tailed).

4.0 DISCUSSION

4.1 Summary of the main findings

This study has compared the cognitive performance of a group of adults with PKU who have been early and continuously-treated until adolescence, with a group of healthy control participants matched for age, sex, IQ, and years of education. The results suggest that the PKU and control groups are not significantly different on dimensions of age, gender, years of education, or IQ, measured by the WASI (Wechsler, 1999). Furthermore, there were no significant differences between the two groups on the self-report measures of depression and anxiety (the Beck Depression Inventory and the Beck Anxiety Inventory), or on the self-report measure of quality of life (the SF-36). This suggests that the groups were well-matched on these variables, and these are unlikely to confound the analyses of group differences on the cognitive measures. Performance on the neuropsychological measures was estimated from indicators of both correctness of responses and reaction times for each of the tasks in question. Thus, comparisons between groups were based on both accuracy and speed of performance.

The first hypothesis stated that adults with currently untreated PKU who have been early and continuously treated throughout childhood will be significantly impaired in the efficiency with which they can process higher working memory loads in comparison to matched controls participants from the normal population. To test this hypothesis the PKU and control groups' performance was compared on the two working memory tasks (the unpaced nback and paced nback tasks). Firstly, group

comparisons were made on the unpaced nback task, which required participants to respond to stimuli according to a rule and in their own time. Due to these parameters of the task, any difference in performance between the two groups would be likely to be evident in reaction times, as participants would tend to respond more slowly to maintain accuracy. There was also a significant effect of group in reaction time comparisons in the predicted direction as the PKU group were responding more slowly than the control group. There was no interaction effect between group and task suggesting that the groups did not differ significantly in the extent to which their performance deteriorated as the working memory demands of the task increased.

Furthermore, group comparisons were made on the paced nback task, in which stimuli were presented for a certain amount of time, which limited the period in which a response was required. Any group differences would be likely to be apparent in the level of accuracy achieved on this task, as the speed of response would need to be maintained at a level at which participants could keep up with the presentation of stimuli. As predicted there was a significant effect of group in terms of accuracy on the paced task, where the PKU group were performing less accurately on this time-limited task than the control group. There was no interaction effect which suggests that the PKU group' performance did not decrease to a greater extent than the control group as the working memory demands of the task increased.

Overall, these findings are consistent with predictions as the PKU group performed worse on the working memory task, which was expected to be sensitive to the selective deficits that have previously been demonstrated in PKU. However, one might also have expected a significant interaction between group and task, as the

literature suggests that people with PKU have particular problems with processing information with a high working memory load so one might have expected their performance to deteriorate more than the control group as the working memory demands of the task increased. This issue will be discussed in more detail later in this chapter.

The second hypothesis predicted that those with PKU would not show significantly poorer performance than the control participants in a task tapping another executive function, reward-based learning, which is thought to be less reliant on the dorsolateral prefrontal cortex. To test this hypothesis comparisons were made of the two groups' performance on the Object Alternation task, which is purported to tap reward-based learning ability. Comparisons of participants' success at this task were based on the number of trials where responses were correct and whether participants achieved 5 consecutive correct trials, as this suggests that they may have learned a successful strategy. These criteria are similar to those used in previous studies employing a similar task (Chorover & cole, 1966; Freedman, 1990; Freedman & Oscar-Berman, 1986; Gansler et al., 1996). Reaction times as an indication of speed of responding were analysed as another measure of performance on this task so as to strengthen the test of group differences. Group comparisons suggest that the groups did not display significantly different performance on any of these indicators, which confirms the predictions of the second hypothesis and suggests preserved ability in reward-based learning on the part of the PKU participants.

Thirdly, the performance of the two groups was compared on the two conditions of the perceptual task, (shape matching and association matching) which require forced-

choice perceptual judgements. This is suggested to make relatively fewer demands on executive functions than either of the other two tasks examined. Analyses revealed no significant difference between the performance of the two groups on either speed or accuracy of performance on either of the perceptual tasks. This is consistent with the predictions made by the third hypothesis, suggesting that the PKU participants were able to perform to the level of matched control participants on this relatively non-executive task.

Finally, there was no correlation between the PKU group's concurrent Phe levels and their performance on the working memory task. This is inconsistent with the fourth hypothesis which predicted a negative correlational relationship between Phe levels and task performance as there is some evidence to suggest that the higher the concurrent Phe levels, the greater the level of dopamine depletion in the brain and thus the greater the extent of impairment in executive functioning. However, as stated in the Introduction section, many previous published studies have also failed to show significant correlations on the basis of concurrent Phe levels, which may be explained by several other variables which may confound the finding of a relationship.

4.2 Issues with regards to the internal and external validity of the findings

In order to provide a context for the interpretation of these findings, it is worth considering the representativeness of the PKU group sampled in this study and the issue of analysing speed and accuracy as separate indicators of performance on the tests. These will be considered in turn in more detail below.

4.2.1 Characteristics of the PKU group sampled in this study

The characteristics of the PKU group sampled in this study have been considered in terms of how comparable they are to those with PKU sampled in published studies. Firstly, the concurrent blood Phe levels obtained by the PKU group in this study, and the mean age at which they stopped the diet, in comparison to samples of previous studies. This is difficult as there have been very few studies with a sample of untreated adults with PKU who have been early and continuously-treated throughout childhood and early adolescence. However, Smith, Klim, Mallozzi & Hanley (1996) studied a similar population whose mean concurrent blood Phe level was 1056 μmol/L. Also, Ris et al. (1994) studied a sample of early-treated adults, at least half of whom had not had a history of continuous dietary adherence, and the mean concurrent blood Phe level of their sample as a whole was 1320 μmol/L. In contrast, the mean concurrent blood Phe level of the sample of untreated adults in the present study was 1264.60 μmol/L. Thus, the mean concurrent Phe level of the participants sampled in this study falls between the parameters of previous published studies and is therefore likely to be a broadly comparable sample in this regard.

With so few studies for comparison, it is difficult to draw clear conclusions about the comparability of the sample in the present study, but clearly the Phe levels do not differ a great deal from published studies of this kind of group to date. It is difficult to compare the levels obtained in this studies in the many previous studies with children as there are different blood Phe level limits set for different age groups. However, it is clear that the Phe levels of the sample in this study were significantly

higher than the limit of 700 μmol/L for adults on the diet, so the levels of those in this study were clearly above blood Phe level limits considered to be relatively more protective for the brain (Medical Research Council, 1993b). Given these levels it is likely that predicted selective impairments in PKU may be apparent in the present study. However, previous studies with adults with similar blood Phe levels did not demonstrate such impairments. This difference in findings will be discussed in more detail later in this chapter.

In addition, it may be worth considering the mean Full-Scale IQ of the PKU group, as measured by the WASI (Wechsler, 1999), which was found to be 102.55. In comparison to previous studies with adults with PKU, the IQ of the PKU group sampled in this study appear to be higher than other studies. For example, in Pietz et al.'s (1998) study early and continuously-treated adults with PKU achieved a mean Full-Scale IQ of 98. Most of the other studies of people with early and continuously-treated PKU have been with children, and in these studies IQ's tended to be in the 80's or 90's (Berry et al., 1979; Dobson et al., 1976; Waisbren et al., 1994; Williamson et al., 1981). These studies have not all used the same measures of IQ so this may account for some differences, however it is likely that the Wechsler scale used in the present study would have lead to more conservative estimates of IQ. Thus, it appears that the PKU group sampled in the present study were of a higher IQ in comparison to samples in the published literature. This may be because many of the outcome studies were carried out many years ago and the dietary treatment may not have been as effective as it was when the current participants were on the diet, due to general improvements in treatment and how participants are supported to maintain effective dietary control. Also, those who chose to participate in the study

may be more motivated with regards to the PKU and therefore may have had earlier diagnoses and better treatment in early life, leading to the achievement of higher IQ's. Nevertheless, since the main aim was to compare people with PKU with healthy control participants, who were matched on IQ, this does not have significant implications for the testing of the hypotheses of this study.

The battery of tests used to measure IQ are bound to include some which tap aspects of executive functioning. That is because sub-tests of the battery are selected according to the extent to which they load on the factor of general intelligence, g. Sternberg (1985) has argued that the general intelligence, or g factor, obtained when batteries of mental tests are factor analysed, is a reflection of the fact that executive functions are common to all cognitive tests. However, three lines of evidence fail to support Sternberg's formulation (Crinella, 1999). Firstly, in animal problem-solving studies there is only a modest degree of overlap between brain structures that are critical for g, and brain structures that have been identified as the rodent EF system. Secondly, children with attention-deficit and hyperactivity disorder, characterised by EF dysfunction, do not have IQ scores that are lower, on average, than children in the test standardisation populations. Thirdly, humans with frontal lobe lesions often have clear executive deficits but IQ (as the next-best estimate of g) may be preserved. Furthermore, even if such IQ tests do tap aspects of executive functioning, by matching the two groups on the basis of IQ in the current study, it may be argued that this lessens the likelihood of finding group differences on the tests of specific executive processes. Therefore, it is argued that this study provides a stringent test of the selective executive deficit hypothesis of PKU, which is the main focus of the present investigation.

4.2.2 Performance on tests measured by both speed and accuracy

As described in the Results section, performance on the cognitive tests were measured in terms of both speed and accuracy. Given the intricate relationship between these two indicators of performance, drawing conclusions on the basis of separate analyses of each is considered in more detail here, before a discussion of the detail of the findings. The instructions to the participants on each of the tests indicated the requirement to respond as quickly and accurately as possible, thus no one indicator was prioritised or emphasised more strongly. The problem of how to measure ability on tasks where both speed and accuracy can be measured is well-recognised (see e.g. Kyllonen, 1997; Sanders & Rath, 1991; Wright & Dennis, 1999). This difficulty arises because of patterns of responding which suggest that the time taken to respond to a stimulus depends, in part, on the accuracy of the response. Individuals differ in how they choose to draw a balance between maintaining speed and accuracy (Furnham, 2001; Neubauer, Bauer & Hoeller, 1992). Nevertheless, such individual differences across the sample are not necessarily important when testing for group differences, which was the main aim of this study.

However, this issue highlights the importance of measuring both speed and accuracy in measuring performance between groups as the pattern of results may be complicated by the trade-off between speed and accuracy if either is considered in isolation. A few studies have examined performance in people with PKU on measures of both speed and accuracy (Brunner, Berch & Berry, 1987; Stemerdink et al., 1995; Weglage et al., 1996). However most have measured only reaction times (e.g. Lou et al., 1987a; Lou et al., 1987b). By considering both measures of

performance in the present study, it is argued that this provides a particularly strong test of any group differences as it allows for the possibility that differences in performance on speed and accuracy may reduce the likelihood of finding significant group effects in overall performance. Where group differences proved significant (or non-significant) in spite of this possibility it is likely that the measures used in this study were able to tap clinically significant differences in performance. It is argued that the fact that the differences or lack of them were maintained on both indicators of performance in each task strengthens the test of the selective deficit hypothesis of PKU.

4.3 Performance on the two working memory tasks

The unpaced nback task required participants to respond to stimuli in their own time so as to be most sensitive to differences in speed of responding between the two groups. There was a significant effect of group in reaction time comparisons, in that the PKU group were responding more slowly than the control group. It could be argued that, as there were no group differences on accuracy in this unpaced task, the PKU group may have been maintaining a high level of accuracy by sacrificing speed on this task. Thus, if there were any real differences in performance on this task it is likely that they would be evident in slower reaction times of the PKU group. This is confirmed by the findings that the PKU were significantly slower on the unpaced task than the control group. Analyses also revealed a significant effect of task in terms of accuracy and speed of responding, in that both groups of participants performed less accurately and more slowly as the working memory demands of the task increased. However, there was no interaction effect between group and task, which suggests that the PKU group were not deteriorating in their performance to a greater extent than the control group.

By contrast, in the paced nback task stimuli were presented only for a limited amount of time and did not remain on screen until the participant had made a response so any group differences would be likely to be apparent in the level of accuracy achieved, since the demands of the task ensured participants had to maintain a speed of responding within the limits of presentation of stimuli. In accordance with this prediction, both groups performed less accurately in this paced task as the attentional demands of the task increased. The analyses also revealed significant group

differences, in that participants with PKU performed significantly less accurately on this task than control participants. There was no interaction effect between group and task on the paced task, suggesting that participants with PKU did not deteriorate in performance to a significantly greater extent than control participants as the working memory demands of the task increased.

Overall, the findings of the present study are consistent with some studies which have demonstrated deficits in attention processes in people with PKU (Diamond et al., 1997, Weglage et al., 1996; Welsh et al., 1990, Welsh & Pennington, 2000). However, they are inconsistent with the findings of other studies in which group differences in performance were not found (Griffiths et al., 1998b; Mazzocco et al., 1994; Stemerdink et al., 1994). There are a number of possible explanations for these mixed findings. One difficulty interpreting the differences across studies is caused by the use of different measures sensitive to executive functions. It is therefore uncertain whether the differences in findings are due to task differences. Measurement issues become particularly complicated when working with children because there are no executive tasks that have been neurologically validated, such as where selective deficits have been demonstrated in children with known frontal-lobe dysfunction. In many instances, tasks are purported to be measures of frontal-lobe function because their demands are similar to the demands of the tasks used with adults who have frontal-lobe lesions (Smith, Kates & Vriezen, 1992). For example, Welsh et al. (1990) and Mazzocco et al. (1994) employed tasks whose requirements seemed similar to those used with adults with frontal-lobe dysfunction. Mazzocco et al. (1994) examined performance of school-age children with PKU on six measures of executive function (Tower of Hanoi, Visual Search, Figural Fluency, Matching

Familiar Figures, Wisconsin Card Sorting and Contingency Naming) plus three discriminant measures of visuo-spatial functioning. The results indicated that children with PKU did not differ from matched controls on any of the measures, leading the authors to suggest that early-treated PKU leads to delays in the development of executive function skills rather than absolute and lasting deficits. In addition, Stemerdink et al. (1994) used tasks sensitive to information processing deficits; however, it is unclear to what extent these tasks had an executive component.

However, Griffiths et al. (1998b) compared 11 school-age children with PKU to matched control participants on the one-back and two-back versions of the Continuous Performance Test, for which there is some evidence of an association with dorsolateral prefrontal cortex functioning (Barch et al., 1997; Perlstein, Carter, Noll & Cohen, 2001; Stern, Sherman, Kirchoff & Hasselmo, 2001) and which has some similarities to the nback task used in the present study. The PKU group in the sample were early and continuously-treated children with a mean age of 8.83 years. These authors measured both accuracy and speed of response and did not find significant differences in performance between the groups. These authors concluded that the on-diet PKU children could concentrate, or conversely, resist distraction, as well as their non-PKU counterparts. In this sample the average pre-school and school-age Phe levels for the participants with PKU sampled in this study fell within the UK guidelines so these children may not have been exposed to particularly high Phe levels. Although this version of the task is not exactly the same as the task used in the present study, it has many similarities so it is unlikely that task differences alone can account for this inconsistency in findings. However, in Robbins' review

paper (2000) he suggests "the precise nature of the cognitive task under study is shown to be a powerful determinant of the effects of mesofrontal dopamine depletion in monkeys" (p. 130). It may the case that subtle differences in task demands lead to differences in findings when testing for subtle deficits.

Nevertheless, it can be argued that the present study is a more stringent test of the selective executive deficit hypothesis of PKU as the tasks used have been validated in research using a variety of methodologies as being selectively associated with dorsolateral prefrontal functioning, and have been validated with a similar age group to those sampled. Thus, this may represent a more robust test of the selective executive hypothesis of PKU, with the current findings suggesting more selective impairments in cognitive functioning in adults with PKU than has been suggested by the studies with children.

As there was no evidence of a significant interaction effect between task and group on either of the working memory tasks, there was no justification for analysing group differences on each condition of the task separately (i.e. the 0-, 1-, and 2-back conditions). Thus, whilst the PKU group were performing more slowly and less accurately than the control group on this working memory task, the findings do not suggest that the PKU group's performance got worse to a greater extent than the control group as the working memory demands of the tasks increased. This latter finding may be considered to be inconsistent with the predictions made on the basis of literature reviewed in the Introduction section, which suggests that people with PKU are likely to demonstrate the most severe deficits on tasks with the highest working memory load.

There are several explanations for the finding of a lack of interaction effects. Firstly, performance on IQ tests is dependent on a variety of cognitive processes, including executive functions. Evidence suggests that even well-treated children with PKU have been shown to achieve lower IQ's than their unaffected siblings, which suggests that cognitive impairments resulting from PKU are having an effect on obtained IQ scores. As the groups were matched on IQ in the present study, it can be argued that the design of this study is particularly stringent in testing for group effects, as this lessens the likelihood of finding significant differences in executive functions between the two groups.

However, from a theoretical perspective the lack of interaction effects in this study appears to suggest that the selective executive deficits in PKU may therefore be most apparent on tasks requiring selective attention in the context of some working memory demands (which arguably requires some executive processes). It may be that the cognitive performance of adult participants with PKU is not so impaired by the extent of working memory demands per se, in comparison to the studies with children. This finding may be interpreted as demonstrating more specific deficits than have been found in the studies with children. This may be due to the particular effects of deficient neurotransmitter synthesis in particular neuronal networks within the PFC (which may differ to that of children and animals studied in the published literature). There is evidence of specific functions, such as error signals, in selective attention and vigilance (Aston-Jones et al., 1991), and specificity of neurochemical effects. For example, depletion of mesolimbic dopamine (Cole & Robbins, 1989) and forebrain serotonin (Harrison et al., 1997) appear to effect speed and probability of

responding without affecting accuracy, and mesostriatal dopamine loss only leads to significant deficits in accuracy under certain conditions (Baunez & Robbins, 1999). Thus, it may be the case that many neurochemical systems are implicated in efficient performance and they modulate performance in different ways (Robbins, 2000). Also, as Robbins (2000) has suggested, the effects of dopamine modulation depends upon many factors such as the nature of the task under study.

Furthermore, performance may also be affected to some extent by the level of difficulty of the task (as performance in some 'easy' tasks appears to be improved with higher levels of stress or arousal), and also by individual differences in people's capacity to perform accurately (Granon et al., 2000). This begs the question of exactly what cognitive processes are involved in performance on the nback task, as the participants with PKU did not appear to show any attentional deficits which impaired their performance on the other tasks in the present study.

There appears to be a number of processes involved in nback task performance, some of which are affected by working memory capacity and others which are not. It may be the case that the demonstrated activation in particular regions of the dorsolateral prefrontal cortex interacts with the modulatory effects of dopamine in such a way that there is not a straightforward relationship between dopamine depletion in PKU and deficits in capacity for processing information with a high working memory load. Also, the exact nature of the pathologic effects of high levels of Phe on the brain is not yet clear (Pratt, 1982; Surtees & Blau, 2000; Huttenlocher, 2000). Therefore, the possibility that the selective executive impairments in PKU are more evident in

executive aspects of selective attention than in working memory per se cannot be ruled out.

4.4 Performance on the Object Alternation task

The second hypothesis predicted that participants with PKU would not show significant impairments in the Object Alternation task, which taps another executive function of reward-based learning, which is thought to be less reliant on the dorsolateral prefrontal cortex, compared to healthy control participants. Analyses revealed no significant differences on any indicators of performance in this task between the two groups under study. This suggests that the PKU group did not demonstrate significantly impaired performance, relative to control participants, on a task argued to tap reward-based learning ability as an alternative aspect of executive functioning.

This task has been consistently linked to cognitive processes of reward-based or associative learning, which has been associated with the orbitomedial PFC (Mishkin, Vest, Waxler & Rosvold, 1969; Chorover & Cole, 1966; Freedman, 1990; Freedman & Oscar-Berman, 1986; Freedman, Black, Ebert & Binns, 1998; Gansler, Covall, McGrath & Oscar-Berman, 1996; Abbruzzese, Ferri & Scarone, 1997; Seidman et al., 1995; Zald, Curtis, Folley & Pardo, 2002; Curtis, Zald, Lee & Pardo, 2000). The lack of group effects on this task may therefore suggest that those with PKU are unimpaired in reward-based learning, compared to control participants. There is considerable evidence linking the alternation task to functioning within the orbitofrontal cortex in both animal (Mishkin, Vest, Waxler & Rosvold, 1969) and

human lesion studies (Freedman, Black, Ebert & Binns, 1998). Furthermore, functioning within the orbitofrontal cortex, on the basis of performance on similar alternation tasks, has been shown to be dissociable from functioning in tasks tapping the dorsolateral prefrontal cortex (Rolls, 2000). Evidence has accrued which supports the hypothesis of dissociable neurochemical systems as well as anatomical systems in respect of the distinction made above, particularly in studies comparing the performance of patients with Alzheimer's disease (which is thought to be associated with the orbitofrontal system) and Parkinson's disease (which is thought to be associated with the dorsolateral system) (Freedman, 1990; Freedman & Oscar-Berman, 1986). This is consistent with the hypothesis that the neurochemical effects observed in PKU may not lead to impaired functioning within the orbitomedial PFC, which has been shown to be less sensitive to fluctuations in dopaminergic neurotransmission (Rolls, 2000).

Thus, it may be argued that patients with PKU are unlikely to demonstrate impairments on an associative learning task, given the hypothesised specificity of cognitive deficits and their associated specific neurochemical and anatomical systems. This hypothesis was confirmed by the finding of no significant group differences between participants with PKU and matched healthy control participants on the Object Alternation task. Furthermore, given this finding with respect to measures of both speed and accuracy, it is suggested that the participants with PKU did not perform more slowly on all tasks, which supports the idea that this is not a generalised impairment of slower information processing and responding.

4.5 Performance on the perceptual tasks

The third hypothesis suggested that the patient and control groups would perform comparably on a task which places minimal demands on executive functions, which was tested by comparing performance on the perceptual task. Analyses of performance on the perceptual tasks suggest that the groups demonstrated comparable performance, which is in accordance with the predictions. It could be argued that, due to the relative simplicity of this task, performance of both groups reached a ceiling level and that therefore this task was not sensitive enough to tap subtle deficits that may be apparent in the performance of the PKU group. However, given that performance was measured in terms of speed as well as accuracy, there was still scope for differences in reaction times between the groups, even though accuracy was maintained at a high level by both groups. As no group differences were found on either measure of performance, and on either perceptual task, it is suggested that the findings provide fairly strong support of the hypothesis of a lack of group differences on this task, which is purported to make relatively minimal demands on executive functions, compared to the other two tasks presented. This confirms the prediction made in the Introduction section and supports the argument that people with PKU show preserved abilities on tasks which do not depend to such a great extent on the prefrontal cortex, but instead mainly tap functions subserved by the parietal cortex. This is consistent with the hypothesis that cognitive impairments in PKU do not extend to abilities which place only minimal demands on executive functions which are most dependent on the prefrontal cortex. Furthermore, given the lack of group differences on measures of both speed and accuracy in the perceptual

tasks, the participants with PKU do not appear to be performing more slowly on all tasks, which supports the idea that the impairments in PKU are not generalised deficits in speed of information processing and responding.

4.6 Relationship between dietary history, Phe levels and performance on cognitive tasks

Firstly, there was no evidence of a significant relationship between participants' concurrent blood Phe levels and performance on the cognitive tasks in the present study. The fourth hypothesis predicted that there may be a negatively correlated relationship, with higher Phe levels being associated with poorer performance. However, as discussed in the Introduction section, there are mixed findings in the literature with regards to evidence of such a relationship. Some studies have demonstrated such a relationship (Diamond et al., 1997; Pietz et al., 1998; Ris et al., 1994; Smith et al., 1996; Weglage et al., 1996; Welsh et al., 1990), but others have not (Griffiths, Campbell & Robinson, 1998; Griffiths, Tarrini & Robinson, 1997).

However, there are several factors confounding the comparison between different studies. Firstly, due to differences in age between different samples, and the fact that there are different levels of blood Phe recommended for different age groups, comparing blood Phe levels between different samples studied is not straightforward. Furthermore, the effects of blood Phe levels on cognitive performance is complicated by levels of IQ, the age at which diet was started and stopped, the level of adherence to diet, and individual differences in the extent to which dietary control is able to reduce blood Phe levels. For example, treatment continuity has been shown to make

a difference to problem-solving ability (Brunner, Jordan & Berry, 1983) and reaction times (Lou et al., 1987; Krause et al., 1985; Schmidt et al., 1994), but there are exceptions to this (Jordan et al., 1985). Blood phe levels have been shown to be more strongly related to performance than IQ (Welsh et al., 1990; Diamond et al., 1997). However, the lower the IQ, the less the effect on performance after reducing Phe levels (Krause et al., 1985). Additionally, as described in the Introduction section, there is some evidence to suggest that cognitive impairments in adults are mediated in part by lifetime blood Phe levels (Pietz et al., 1998; Smith et al., 1996; Ris et al., 1994). For example, Pietz et al., (1998) demonstrated that both concurrent Phe levels and Phe levels from the age of 12 onwards were related to performance on an attention task.

The equivocal findings on this issue of the relationship between blood plasma Phe levels and cognitive performance is further complicated by the fact that blood Phe levels are only an indirect measure of brain Phe levels (see e.g. Koch et al., 2000) and the technology to measure brain Phe levels directly is still being developed. However, stopping the diet or Phe loading has been shown to lead to decreased levels in the neurotransmitter metabolite 5-HIAA (Lou et al., 1985) and dopamine (Krause et al., 1985) in patients with PKU. These decreases have been shown to be related to slower reaction times on tests of sustained attention and higher integrative functions. There is a body of evidence supporting the conclusion that a decrease in sustained attention ability may be due a decrease in neurotransmitter synthesis.

Thus, there is evidence of a relationship between sustained attention and concurrent blood Phe levels, with partial reversibility of deficits when patients are returned to a

strict diet (Schmidt et al., 1994; Schmidt, Burgard & Rupp, 1996). In Schmidt et al.'s (1994) study the mean concurrent blood Phe levels of treated young adults were around one and a half times the recommended limit. Additionally, Krause et al. (1985) found a relationship between concurrent blood Phe levels and length of reaction times in 10 patients with PKU (ranging from ages 6 to 24) whose levels rose to under one and a half times the recommended limits. In the current study with older untreated adults the mean blood Phe levels were almost two times above the recommended limit and there was no significant association between concurrent Phe levels and test performance. However, in contrast to the studies reviewed above, the patients in the present sample had been untreated for much longer periods which may complicate a comparison. It may be the case that for the current sample of patients with PKU lifetime blood Phe levels bear a closer relationship to performance than concurrent blood Phe levels. This may be because when concentration of Phe in the blood reaches a saturation point, which varies between individuals, there are additional toxic effects of the accumulation of Phe (Seakins et al., 1982). This may make concurrent blood Phe levels less straightforward as an indication of the extent of effect of high Phe levels on the brain. Thus, the subtle cognitive impairments evident in the PKU group in this study may have been mediated by lifetime blood Phe levels in the current sample of participants with PKU.

4.7 Theoretical implications of the findings of the current study

In the current study selective deficits were demonstrated in the efficiency of processing information requiring higher attentional demands, but not tasks sensitive to other types of executive and non-executive processes. This pattern of results was maintained despite comparison to a control group matched on age, sex, IQ, and educational history. This suggests that, despite early and continuous treatment throughout childhood, the brain is not necessarily protected from subtle damage by dopamine depletion to the brain as a result of high Phe levels. This finding confirms aspects of the hypothesis of a selective executive deficit PKU and extends its support with evidence of such deficits in adults with untreated PKU. This is contrasted with the findings of more generalised cognitive deficits in other studies with adults with PKU (Ris et al., 1994), and studies where such deficits in adults have not been found (Griffiths et al., 1998b; Mazzocco et al., 1994; Stemerdink et al., 1994).

However, due to a lack of finding of significant interaction effects as the working memory demands of the task increased, these findings do not support the hypothesis that ability to process information in PKU is most impaired by the extent of demands on working memory. These findings are inconsistent to some extent with Petrides' model (1994). He proposed that the mid-dorsolateral PFC (areas 46 and 9/46) is a specialised region for the on-line monitoring and manipulation of cognitive representations within working memory, as opposed to the ventrolateral PFC which is associated with active selection, comparison and judgement of stimuli held in short and long-term memory. He has argued that these represent two levels of executive control which are probably involved in several tasks and often simultaneously. He

has shown that, in the nback task, dorsolateral PFC activation differed from ventrolateral PFC activation in maintaining working memory content (Callicott et al., 2000).

The finding of group differences supports the idea that patients with PKU are selectively impaired on monitoring information in the context of a working memory task. However, the current findings are inconsistent with the evidence that the number of stimuli that need to be monitored and not the maintenance of information or passage of time per se is the critical variable affecting the performance of monkeys with lesions to the mid-dorsolateral PFC (Petrides, 1995a, 1995b; Petrides, 1998), as in the current study, the performance of the PKU participants did not deteriorate to any greater extent than that of the control group as the number of stimuli that needed to be remembered increased. Instead, there were differences between the groups on the working memory task overall.

The findings of the current study are also inconsistent to some extent with Diamond et al.'s (1997) hypothesis that selective deficits in PKU are apparent when working memory is required. Nevertheless, the participants with PKU performed significantly worse on measures of both accuracy and speed of responding on this task. As this task has been shown to be associated with the functioning of the dorsolateral PFC, the fact that deficits were only apparent on tasks tapping this region, as opposed to an executive task tapping another region of the PFC, supports Diamond et al.'s (1997) hypothesis that the neurochemical changes in PKU will have a particular impact on functions dependent on the dorsolateral PFC, due to the special sensitivity of this area of the brain to mild fluctuations in levels of dopamine.

The present findings are consistent with Welsh's (1996) finding that patients with PKU were selectively impaired, in comparison to healthy control participants, on a selective attention task. As discussed above, these findings support an explanation of selective deficits in attentional processes, in people with PKU. This may be the case only in tasks for which functioning is associated with the dorsolateral prefrontal cortex, such as nback task, as these attentional deficits were not apparent in the Object Alternation task, which taps executive processes relying on the orbitofrontal cortex, or on a control task which places minimal demands on executive functions.

In summary, it is argued that the findings of significant group differences in performance in the nback task, tapping dorsolateral prefrontal cortex functioning, and not on the Object Alternation Task, tapping orbitomedial functioning. support the hypothesis of a selective executive deficit in people with PKU on tasks sensitive to impairments in functioning within the dorsolateral prefrontal cortex (and its associated dopaminergic systems). These findings provide support for aspects of the selective executive deficit hypothesis in PKU in which the neurochemical changes in PKU are thought to have a particular impact on dopamine neurons within the dorsolateral PFC and therefore people with PKU are expected to be selectively impaired on tasks tapping functions associated with this region of the brain (Diamond et al., 1997; Weglage et al., 1996; Welsh et al., 1990, Welsh & Pennington, 2000). Furthermore, it may argued that such a finding is consistent with the model of O'Reilly et al. (2002) in which it was suggested that there is a dissociation between these two areas and a fractionation of executive functioning in which processing information with higher attentional demands is separable from functions requiring reward-based learning. Thus, despite early treatment with a well-

controlled diet, subtle deficits may remain, in particular in selective attention, which has been argued to rely on intact functioning within the dorsolateral prefrontal cortex.

4.8 Clinical implications of the findings of the present study

It is evident from the findings of this study that the group of untreated adults, whose concurrent blood Phe levels were well over the recommended limits, were performing as well as controls in several respects, and there is evidence of only subtle executive impairments. This is important for people with PKU, such as untreated adults sampled in the present study, many of whom are struggling with the issue of whether or not to return to the diet. These people have often been off the diet since early adolescence so the prospect of returning to the diet, in accordance with current medical recommendations, would require a major lifestlye change which may have emotional, social and financial costs. These patients must consider whether the findings of subtle deficits in adults are important enough for them to make this lifestyle change, despite the fact that there is evidence of preserved functioning in many other types of tasks.

Furthermore, there were no differences between the two groups in this study on any of the measures of pyschiatric and dysexecutive symptomatology which suggests that the PKU group sampled appeared to have been functioning well overall, despite having been off-diet since early adolescence. This is consistent with the few studies with adults which have suggested that early-treated PKU-affected adolescents and adults do not show a higher risk for emotional and behavioural disturbance compared to appropriate control participants and there is no evidence of a pattern of adjustment problems in adolescents with PKU (Sullivan, 1999). Nevertheless, given the paucity

of studies available it is argued that there is a need for multidisciplinary follow-up studies of adult adjustment, utilizing a biopsychosocial approach to further the understanding of the impact of a lack of long-term phenylalanine control and illness-related stress (Sullivan and Chang, 1999).

Nevertheless, given that the dietary treatment involves a great investment of time and effort which has an impact on people's lifestyles, it is important for patients and clinicians to have evidence on which to base their decisions about whether or not they feel it is worth trying to return to the diet. As there is only very limited evidence from studies of early and continuously-treated adults with PKU, the findings of this study are important in that they shed light on the apparently selective executive deficits existing in this group, in the context of preserved abilities in other executive and non-executive domains.

These findings may suggest that remaining untreated does not appear to be having a great impact on the lives of these adults with PKU, which supports the effectiveness of the treatment received early in life and the recommendations received at the tiem that coming off the diet in adolescence was sufficient to prevent later problems. However, there may be some areas of life in which subtle deficits observed could have an impact. For example, there are certain jobs for which abilities of good sustained and selective attention are essential, such as a stock market trader or a nurse. Furthermore, the impairments observed could have implications for other aspects of life where attention to detail, accuracy and speed of response are necessary, such as in a nursing role, dealing with complex finances, looking after young children and so on. Difficulties in these areas could also be important in

managing the disorder in day to day life as people are required to watch carefully what they are eating, make careful measures of powders for supplements, and take regular and accurate blood spot tests independently. It would be important for clinicians and pharamceuticals companies who develop treatment packages to bear these issues in mind so as to make it as easy as possible for people to manage their treatment well.

For those who remain untreated, as those in the present study, careful decisions will need to be made in the light of new evidence. People with PKU may need to consider the impact of such cognitive difficulties may have on their work and their life, so that they can make allowances, whether or not this means returning to the diet. If such people were to seek help from services they may be helped to develop strategies to manage their cognitive difficulties, such as writing things down, avoiding trying to do two tasks at once, and taking extra time when managing complex information, such as breaking it down into chunks. Advising on use of such strategies could follow an approach similar to that used in brain injury rehabilitation settings (Prigatano, 1999).

4.9 Limitations of the current study and suggestions for future research

Further studies in this area, using equally sensitive measures, adequate control tasks and robust sample sizes, may be necessary to further the understanding of the extent to which the findings of this study may be generalised to those with higher or lower blood Phe levels, and different treatment histories. Given the individual variability in blood Phe levels, dietary adherence and duration, it is unprofitable to consider those

with PKU as a homogenous group. For example, it would be interesting to consider in more detail whether the age at which adolescents come off the diet can be demonstrated to have a relationship with the extent of cognitive deficits. It may be useful to study adults with treated PKU and lower blood Phe levels, as it would be interesting to determine whether a matched group of people on-diet also experience similar selective executive deficits.

However, the practical reality appears to be that even adults with PKU who remain on diet often do not achieve blood Phe levels within the recommended limits and clinical experience at the PKU clinic from which this sample was recruited suggests few people are able to manage within these limits. However, if able to recruit a sufficient sample of well-treated adults, such investigations may help to shed light on the issue of the extent to which the dietary treatment can be effective in protecting against such cognitive deficits. Such research could shed light on the clinical effectiveness of the 'diet for life' policy. To some extent the current findings support this policy as some deficits were observed, but their clinical significance will need to be examined further, taking into account individuals' personal circumstances.

4.10 Conclusions

The findings of this study suggest that adults with early and continuously-treated PKU, but who have remained untreated since adolescence, have selective executive deficits in attentional control in teh context of an active working memory task. This supports the selective executive deficit hypothesis of PKU to the extent that these impairments were only observed on a task sensitive to the dorsolateral prefrontal

cortex, where neurons have been shown to be especially sensitive to mild fluctuations in dopamine neurotransmission. As participants with PKU did not demonstrate impaired performance on another task of executive functioning requiring reward-based learning, these findings also support hypotheses of dissociable executive functions, which are subserved by different regions of the prefrontal cortex and the associated neurochemical systems on which they rely. The findings of largely preserved cognitive and emotional functioning in the PKU gorup are argued to support the clinical effectiveness of the childhood treatment programme for PKU. However, the evidence of selective executive impairments may still have implications for those considering returning to diet, in accordance with current U.K. guidelines. Further studies, especially with early and continuously-treated adults may help to evaluate the effectiveness of the 'diet for life' policy. Such findings may also aid patients and clinicians in understanding the implications of remaining untreated in adulthood for their everyday lives.

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APPENDIX A

Questionnaires

Health Screen Interview
Beck Depression Inventory
Beck Anxiety Inventory
DEX questionnaires for self- and independent-rater
SF-36v2 Health Survey

HEALTH SCREENING INTERVIEW

Name _____
Address _____
_____
_____

Telephone No. _____

Sex? Male / Female Date of Birth? _____ Right- or left-handed? _____

Language fluency

Is your first language English? Yes/ No
If not, how fluent are you in English? _____
If not, please tell me all the languages you speak _____
_____
What age did you start to learn each one? _____
_____
_____

Do you have difficulty understanding conversations because of your hearing? Yes/ No
Do you have trouble with your vision that prevents you from reading ordinary print, even with glasses on? Yes/ No
Have you ever been diagnosed as having dyslexia? Yes/ No
Do you have difficulty in using your fingers for fine movements, such as doing up buttons? Yes/ No
Do you have any physical disabilities? _____
_____
_____
_____

Educational and occupational history

What type of school did you attend? _____
Did you have any special schooling needs? _____
If Yes, please give details _____
Did you have a Statement of special educational needs? _____
What age did you leave school? _____
What qualifications did you obtain at school? _____
_____
_____
What qualifications, if any, did you obtain after leaving school? _____
_____
_____
_____
How long was the course of study? _____
Full-time or part-time? _____
What are the main types of work you have done (if any)? _____
_____
_____
_____
What is your main job now? _____
_____
_____
How long have you held this job? _____
Has your work changed as a result of your illness/injury? _____
_____
_____

Health history

Have you ever had a serious illness? Yes/No
If Yes, please give details_____

Have you ever had heart trouble? Yes/No_____
If Yes, please give details_____

Have you ever had a serious accident? Yes/ No
If Yes, please give details_____

Have you ever been unconscious? Yes/ No
If Yes, how many times have you been unconscious? _____
For how long each time? _____

Why? _____

How long was the gap between losing consciousness and your first memory?_____

How long was the gap between losing consciousness and beginning to remember everyday details normally?_____

Have you ever had an operation under general anaesthetic? Yes/ No
Yes, please give details_____

Have you ever had to stay in hospital for any reason? Yes/ No
Yes, please give details_____

Have you ever had:
Meningitis Yes/ No
Encephalitis Yes/ No
Diabetes Yes/ No
Tuberculosis (TB) Yes/ No
Epilepsy/seizures/fits Yes/ No
please give details_____

Are you currently taking any prescribed medication? Yes/ No
please give details _____

Do you take any recreational drugs?

Have you taken any in the past?

Have you ever received treatment for mental or emotional problems? Yes/ No
If Yes, please give details

Injury or illness affecting the brain

Name of your consultant
Consultant's address

Name of your GP
GP's address

Detailed description of injury/illness

When did the injury/illness occur?

At which hospital(s) were you treated? (Full name and address if possible)
Inpatient care

Outpatient care

To your knowledge, did you have: An MRI brain scan? Yes/No A CT brain scan ? Yes/No
If Yes, at which hospital?

When was the scan done?

Have you suffered any problems since, such as difficulties with memory, problem-solving or planning? If so please give details

Is there any other important details about your medical history that I have not asked you about?

BDI-II

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

_____ Subtotal Page 1

Continued on Back

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11. Agitation

0 I am no more restless or wound up than usual.

1 I feel more restless or wound up than usual.

2 I am so restless or agitated that it's hard to stay still.

3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.

1 I am less interested in other people or things than before.

2 I have lost most of my interest in other people or things.

3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.

1 I find it more difficult to make decisions than usual.

2 I have much greater difficulty in making decisions than I used to.

3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.

1 I don't consider myself as worthwhile and useful as I used to.

2 I feel more worthless as compared to other people.

3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.

1 I have less energy than I used to have.

2 I don't have enough energy to do very much.

3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.

1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.

2b I sleep a lot less than usual.

3a I sleep most of the day.

3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.

1 I am more irritable than usual.

2 I am much more irritable than usual.

3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.

1a My appetite is somewhat less than usual.

1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.

2b My appetite is much greater than usual.

3a I have no appetite at all.

3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.

1 I can't concentrate as well as usual.

2 It's hard to keep my mind on anything for very long.

3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.

1 I get more tired or fatigued more easily than usual.

2 I am too tired or fatigued to do a lot of the things I used to do.

3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I am much less interested in sex now.

3 I have lost interest in sex completely.

_____ Subtotal Page 2

_____ Subtotal Page 1

_____ Total Score

BAI®

NE _____ DATE _____

w is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by each ptom during the PAST WEEK, INCLUDING TODAY, by placing an X in the corresponding space in the column next to each symptom.

	NOT AT ALL	MILDLY It did not bother me much.	MODERATELY It was very unpleasant, but I could stand it.	SEVERELY I could barely stand it.
1. Numbness or tingling.				
2. Feeling hot.				
3. Wobbliness in legs.				
4. Unable to relax.				
5. Fear of the worst happening.				
6. Dizzy or lightheaded.				
7. Heart pounding or racing.				
8. Unsteady.				
9. Terrified.				
10. Nervous.				
11. Feelings of choking.				
12. Hands trembling.				
13. Shaky.				
14. Fear of losing control.				
15. Difficulty breathing.				
16. Fear of dying.				
17. Scared.				
18. Indigestion or discomfort in abdomen.				
19. Faint.				
20. Face flushed.				
21. Sweating (not due to heat).				

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Dex Questionnaire
Self-rating

Thames Valley Test Company

Subject's name

Date

This questionnaire looks at some of the difficulties that people sometimes experience. We would like you to read the following statements, and rate them on a five-point scale according to your own experience:

1 I have problems understanding what other people mean unless they keep things simple and straightforward

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

2 I act without thinking, doing the first thing that comes to mind

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

3 I sometimes talk about events or details that never actually happened, but I believe did happen

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

4 I have difficulty thinking ahead or planning for the future

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

5 I sometimes get over-excited about things and can be a bit 'over the top' at these times

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

6 I get events mixed up with each other, and get confused about the correct order of events

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

7 I have difficulty realizing the extent of my problems and am unrealistic about the future

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

8 I am lethargic, or unenthusiastic about things

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

9 I do or say embarrassing things when in the company of others

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

10 I really want to do something one minute, but couldn't care less about it the next

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

11 I have difficulty showing emotion

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

12 I lose my temper at the slightest thing

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

13 I am unconcerned about how I should behave in certain situations

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

14 I find it hard to stop repeating saying or doing things once I've started

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

15 I tend to be very restless, and 'can't sit still' for any length of time

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

16 I find it difficult to stop myself from doing something even if I know I shouldn't

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

17 I will say one thing, but will do something different

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

18 I find it difficult to keep my mind on something, and am easily distracted

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

19 I have trouble making decisions, or deciding what I want to do

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

20 I am unaware of, or unconcerned about, how others feel about my behaviour

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

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Dex Questionnaire
Independent rater

Subject's name	
Date of rating	
Rater's name	
Relationship to subject	

This questionnaire looks at some of the difficulties that people sometimes experience. We would like you to read the following statements, and rate them on a five-point scale according to your experience of _____ [the subject]:

1 Has problems understanding what other people mean unless they keep things simple and straightforward

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

2 Acts without thinking, doing the first thing that comes to mind

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

3 Sometimes talks about events or details that never actually happened, but s/he believes did happen

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

4 Has difficulty thinking ahead or planning for the future

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

5 Sometimes gets over-excited about things and can be a bit 'over the top' at these times

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

6 Gets events mixed up with each other, and gets confused about the correct order of events

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

7 Has difficulty realizing the extent of his/her problems and is unrealistic about the future

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

8 Seems lethargic, or unenthusiastic about things

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

9 Does or says embarrassing things when in the company of others

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

10 Really wants to do something one minute, but couldn't care less about it the next

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

11 Has difficulty showing emotion

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

12 Loses his/her temper at the slightest thing

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

13 Seems unconcerned about how s/he should behave in certain situations

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

14 Finds it hard to stop repeating saying or doing things once started

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

15 Tends to be very restless, and 'can't sit still' for any length of time

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

16 Finds it difficult to stop doing something even if s/he knows s/he shouldn't

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

17 Will say one thing, but will do something different

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

18 Finds it difficult to keep his/her mind on something, and is easily distracted

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

19 Has trouble making decisions, or deciding what s/he wants to do

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

20 Is unaware of, or unconcerned about, how others feel about his/her behaviour

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

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The SF-36v2™ Health Survey

Instructions for Completing the Questionnaire

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

EXAMPLE

This is for your review. Do not answer this question. The questionnaire begins with the section *Your Health in General* below.

For each question you will be asked to fill in a bubble in each line:

1. How strongly do you agree or disagree with each of the following statements?

	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
a) I enjoy listening to music.	○	●	○	○	○
b) I enjoy reading magazines.	●	○	○	○	○

Please begin answering the questions now.

Your Health in General

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
○	○	○	○	○

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
○	○	○	○	○

Please turn the page and continue.

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
O	O	O	O	O

7. How much bodily pain have you had during the **past 4 weeks**?

None	Very mild	Mild	Moderate	Severe	Very severe
O	O	O	O	O	O

8. During the **past 4 weeks**, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
O	O	O	O	O

9. These questions are about how you feel and how things have been with you during the **past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) did you feel full of life?	O	O	O	O	O
b) have you been very nervous?	O	O	O	O	O
c) have you felt so down in the dumps nothing could cheer you up?	O	O	O	O	O
d) have you felt calm and peaceful?	O	O	O	O	O
e) did you have a lot of energy?	O	O	O	O	O
f) have you felt downhearted and depressed?	O	O	O	O	O
g) did you feel worn out?	O	O	O	O	O
h) have you been happy?	O	O	O	O	O
i) did you feel tired?	O	O	O	O	O

10. During the **past 4 weeks**, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
O	O	O	O	O

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a) I seem to get sick a little easier than other people	O	O	O	O	O
b) I am as healthy as anybody I know	O	O	O	O	O
c) I expect my health to get worse	O	O	O	O	O
d) My health is excellent	O	O	O	O	O

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE!

APPENDIX B

Ethics Approval Notices

Approval for wider study (1995)
Request and approval for blood testing (2001)
Request and approval for named researcher (2001)

UNIVERSITY COLLEGE LONDON MEDICAL SCHOOL

Administrative Offices
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UCL MEDICAL SCHOOL

25 May 1995

Please reply to: Mrs Vanessa Revill
Committee Secretary
Joint UCL/UCLH Committee on the
Ethics of Human Research: Committee Alpha
(address as above)

Dr Shelley Channon
Head of Neuropsychology Services
Sub-Department of Clinical Health Psychology
Department of Psychology
UCL

Dear Dr Channon,

Joint UCL/UCLH Committee on the Ethics of Human Research: Committee Alpha

No: 95/2953
Title: Memory and executive function in patients with focal brain dysfunction

I am writing to let you know that I am now able to give the above project Chairman's Approval. You may therefore go ahead with your study.

Please note that it is important that you notify the Committee of any adverse events or changes (name of investigator etc) relating to this project. You should also notify the Committee on completion of the project, or indeed if the project is abandoned. Please quote the above number in any correspondence.

Yours sincerely,

Professor M Hobsley
Chairman

Subdepartment of Clinical Health Psychology
University College London, Gower Street, London WC1E 6BT

Dr. Shelley Channon
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Professor Andre McClean
Chairman
The Joint UCL/UCLH Committees on the Ethics of Human Research
Research and Development Directorate
1st Floor, Vezey Strong Wing
112 Hampstead Road
London NW1 2LT

18th June 2001

Dear Professor McClean

Re: 95/2953 Memory and executive function in patients with focal brain dysfunction

As part of the above project, I am studying patients with phenylketonuria. In relation to this, it is important to take account of their concurrent phenylalanine levels, which are obtained from a simple blood test. It is routine research practice in the field to measure this on the day of testing. At present our information sheet specifies that the study does not involve procedures such as taking blood.

These patients are under the clinical care of Dr. Philip Lee, Consultant in Metabolic Medicine. Those who carry out the study on the day of a routine clinic appointment will already have blood taken, as a normal part of their clinical care. For the remainder, we do not wish to take blood ourselves, but rather to send patients to the blood clinic under Dr. Lee's direction. A few patients may prefer to do their own blood spot test, since many of them do this routinely at home.

I should like permission from the Committee to ask patients to undertake a blood test, whether in the blood clinic or by testing themselves. I enclose an amended Information Sheet. I also enclose our standard consent form, but I do not believe that amendments are needed for this.

Yours sincerely

Dr. Shelley Channon
Reader in Clinical Neuropsychology

UCL HOSPITALS

The Joint UCL/UCLH Committees on the Ethics of Human Research:
Committees Alpha and A
Research & Development Office
UCLH NHS Trust
1st floor Vezey Strong Wing
112 Hampstead Road
London NW1 2LT

PROTOCOL AMENDMENT RESPONSE

Study reference: **95/2953**	Principal Investigator's name: **Dr SL Channon**
Study title: **Memory and executive function in patients with focal brain dysfunction**	

PROTOCOL AMENDMENT

Protocol Amendment	Version, date
To ask patients to undergo a blood test (as per your letter dated 18th June 2001)	**New information sheet and consent form (undated and unreferenced)**

Opinion of Ethic Committee: (please indicate one of the following)

(i) **The contents have been noted and the study may continue** ☑

(ii) **Please supply more information about the serious adverse event(s)** ☐

Signature:..... **Date: July 23, 2001**

Print Name: **Iwona Nowicka**

Position in Ethics Committee: **Administrator**

/Please continue on a separate page if necessary/

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Professor André McLean
Chairman
The Joint UCL/UCLH Committees on the Ethics of Human Research
Research & Development Directorate
UCLH NHS Trust
1st Floor, Vezey Strong Wing
112 Hampstead Road
London NW1 2LT

24th September 2001

Dear Professor McLean

Re: 95/2953 Memory and executive function in patients with focal brain dysfunction

Study title: Executive functioning in people with phenylketonuria

I am now conducting a study comparing people with phenylketonuria (PKU) with healthy control participants on a set of cognitive tasks. This work will form the basis of a doctoral dissertation under my supervision for Galya Goodman, who is on the DClinPsy course at UCL. The study involves the use of computerised and pen-and-paper tasks including IQ, executive function and memory, questionnaires and a clinical interview. The participants with PKU are being drawn from Dr. Lee's specialist clinic at Queen Square. The healthy control participants will be recruited from advertisements and from our existing volunteer panel.

I believe that the study falls fully within the remit of my existing ethical permission Ref 95/2953, entitled "Memory and problem-solving in people with focal lesions", since this covers both acquired brain injury and biochemical disorders, and has been amended recently to permit us to ask for a blood sample for participants with PKU. I should be grateful if you could confirm that the new study is fully covered, or let me know of any further information that you wish me to provide.

Many thanks for your help.

Yours sincerely

Dr. Shelley Channon

University College London Hospitals NHS

NHS Trust

Committee Alpha Chairman:
Professor André McLean

Please address all correspondence to:
Iwona Nowicka
Research & Development Directorate
UCLH NHS Trust
1st floor, Vezey Strong Wing
112 Hampstead Road, LONDON NW1 2LT
Tel. 020 7380 9579 Fax 020 7380 9937
e-mail: iwona.nowicka@uclh.org

DR S Channon
Sub-Department of Clinical Health Psychology
UCL
Gower Street

19 October 2001

Dear Dr Channon

Study No: **95/2953** *(Please quote in any correspondence)*
Title: **Memory and executive function in patients with focal brain dysfunction**

Thank you for your letter dated 24th September. I have noted that the following students work under your supervision on the above project: Agnieszka Gunning, Sarah Crawford and Galya Goodman. I also confirm that the new study ("Executive functioning in adults with Tourette's syndrome") is fully covered at this stage, however, your application will have to be renewed in the next year.

Yours sincerely

pp.

Professor André McLean, BM BCh PhD FRC Path
Chairman

Channon19oct/comalpha/aml/ijn/19/10/01

APPENDIX C

Recruitment and correspondence to participants

Letter of invitation to participants
Thank you letter
Information sheet
Consent form
Advertisement for volunteers

Date

Dear Mr,

The Department of Clinical Health Psychology at UCL is currently carrying out research at University College London Hospitals, looking at how people learn, remember and solve problems when they have a variety of medical conditions. As part of this research, we are looking at these skills in people who have phenylketonuria.

It would be of great help and importance if you were to take part. The study has been approved by the local ethics committee and any information given will of course be treated in strict confidence. The study will not influence your clinical management or future care in any way.

Participation in the study involves meeting with a research assistant named Galya Goodman, who works with Dr Shelley Channon. You will be asked to complete a series of psychological tests which measure aspects of learning, memory and problem-solving. The result will be fed back to you in due course.

Galya Goodman will follow up this letter with a telephone call within the next days to ask if there is any possibility that you would be willing to take part. We will be pleased to provide any further details that you require at that time.

We would be very grateful for any help you can give with the study. If you would like to discuss this further with myself please do not hesitate to call via 020 7829 8778.

Many thanks.

Yours sincerely,

Dr Philip Lee
(Consultant in Metabolic Medicine)

Subdepartment of Clinical Health Psychology
University College London, Gower Street, London WC1E 6BT

Dr. Shelley Channon
Director of Project
020-7679-1786

Research Team: 020-7679-5929
Louise Healey
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CONFIDENTIAL

Mrs.

26th September 2001

Dear Mrs. ,

I am writing to thank you for assisting with our research project. Your contribution is greatly appreciated, and we are very grateful for your help.

Our work in this area will continue, and we hope that the findings will contribute towards a greater understanding of the nature and extent of difficulties in memory and reasoning in people who have suffered injury or illness involving the brain.

Thank you once again.

Yours sincerely,

Subdepartment of Clinical Health Psychology
University College London, Gower Street, London WC1E 6BT

Dr. Shelley Channon
Director of Project
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INFORMATION SHEET

Memory and problem-solving study

You are being invited to take part in a study concerned with the ways in which people learn, remember and solve problems. The study aims to examine the nature and extent of difficulties in memory and reasoning in people of different ages, and in those who have suffered injury or illness which involved the brain. This has relevance for everyday living where memory and problem-solving play an important role.

All proposals for research using human participants are reviewed by an ethics committee before they can proceed. This proposal was reviewed by the Joint UCL/UCLH Committees on the Ethics of Human Research.

You will be given a series of psychological tests which measure aspects of learning, memory and problem-solving. These will be arranged to suit your convenience, and you will be able to take breaks if you feel tired. Because of the nature of the study, we cannot give you precise details of the tests, so that this does not influence the findings. You will also be asked a series of questions concerned with the way you are feeling and any difficulties you have been having, and asked to fill out a set of questionnaires.

We are also interested in knowing your current blood phenylalanine (Phe) level. We would therefore like to arrange for you to have this measured on the day we see you. This would involve a brief visit to the blood clinic, in addition to your session with us (unless you are already having a blood test at this time as part of your routine clinic appointment at the Metabolic Unit).

You will be asked to sign a consent form, and any information you give will be treated in strict confidence. You do not have to take part in this study if you do not want to. If you decide to take part you may withdraw at any time without giving a reason. Your decision whether to take part or not will not affect your care and management in any way.

APPENDIX D

Type of occupations of PKU participants and their parents

Type of occupations of PKU participants and their parents

The following table summarises the type of occupation of the participants with PKU and their parents according to the widely used Registrar General's Classification of Occupations (1980) see Argyle, M. (1994). The Psychology of Social Class. London: Routledge (p.7).

Typical occupations of each class:

Professional e.g. accountant, lawyer, doctor, university teacher, scientist.
Intermediate e.g. aircraft pilot, manager, nurse, police officer, school teacher.
Skilled non-manual e.g. cashier, clerical worker, sales representative, secretary.
Skilled manual e.g. driver, butcher, bricklayer, electrician, cook, hairdresser.
Semi-skilled e.g. barworker, hospital orderly, packer, postman, street vendor.
Unskilled e.g. road sweeper, kitchen hand, messenger, office cleaner, labourer.

Participant occupation	Maternal occupation	Paternal occupation
Intermediate	- not given -	- not given -
Intermediate	Intermediate	Intermediate
Intermediate	Intermediate	Skilled manual
Intermediate	Skilled non-manual	Intermediate
In full-time education	Intermediate	Skilled non-manual
Skilled non-manual	Skilled non-manual	Semi-skilled
Skilled non-manual	Intermediate	Skilled manual
Skilled non-manual	Skilled manual	Skilled manual
Skilled non-manual	- not given -	- not given -
Skilled non-manual	Skilled manual	Semi-skilled
Skilled non-manual	Unskilled	Skilled manual
Skilled non-manual	Semi-skilled	Skilled manual
Skilled non-manual	Skilled non-manual	Skilled manual
Skilled non-manual	- not given -	- not given -
Skilled non-manual	Skilled non-manual	Skilled non-manual
Skilled manual	Skilled non-manual	Skilled manual
Skilled manual	Semi-skilled	Skilled manual
Skilled manual	Unskilled	Skilled manual
Semi-skilled	Semi-skilled	Skilled manual
Semi-skilled	Skilled manual	Semi-skilled