Neuropsychological function in adults with early and continuously treated phenylketonuria

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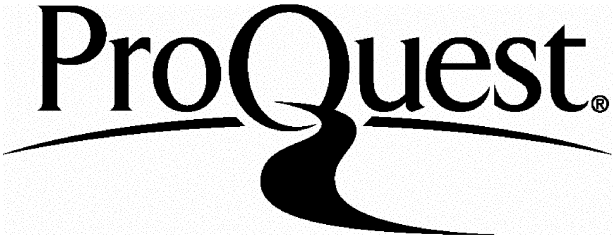

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ABSTRACT

Phenylketonuria (PKU) is an inherited metabolic disease which, if left untreated, usually results in severe learning difficulties. While dietary treatment programmes have greatly improved outcome in PKU, children with treated PKU have been found to be selectively impaired on tests of executive functions. These impairments have been attributed to dysfunction of lateral regions of the prefrontal cortex.

This study investigated whether adults with treated PKU would show cognitive deficits similar to those observed in children, by comparing the performance of 20 adults with continuously treated PKU and 20 matched healthy control participants on a battery of neuropsychological tests. The battery included measures thought to be sensitive to dysfunction of the lateral prefrontal cortex, as well as measures thought to be less sensitive to dysfunction of this region. The results suggested that the PKU participants were selectively impaired on the tests of executive function. These impairments were relatively subtle, and were primarily reflected in increased response times. It is argued that these findings suggest that, despite continued treatment, adults show a selective executive deficit similar to that which has been observed in children. Furthermore, while it is possible that stricter treatment could potentially eliminate this deficit, it is questionable how many patients would be able to achieve the necessary level of dietary control. The implications of these findings for the clinical management of PKU are discussed.

1. INTRODUCTION

1.1 What is PKU?

Phenylketonuria (PKU) is an inherited metabolic disorder which, if left untreated, usually results in the patient developing severe learning disabilities. PKU was first described clinically by Folling in 1934 (see Welsh & Pennington, 2000). Jervis and his colleagues (1939, 1947, 1953; all cited in Knox, 1972) later identified PKU as an inherited metabolic disorder in which there is a deficiency of the enzyme phenylalanine hydroxylase (PAH), which converts the amino acid, phenylalanine (Phe), into another amino acid, tyrosine (Tyr). It is now known that PKU is an autosomal recessively transmitted disorder, involving a mutation of the PAH gene on chromosome 12 (Woo et al., 1985). PKU occurs in approximately 1 in every 10 000 live births in the United Kingdom (Medical Research Council, 1993a), and about 1 in 50 people is a heterozygous carrier (Pietz, 1998). As a result of the deficiency in PAH, blood Phe levels in people with untreated PKU rise to over 10 times normal levels (Diamond, Prevor, Callender & Druin, 1997). The learning disabilities that are seen in people with untreated PKU have conventionally been thought to be the result of the toxic effects of these high Phe levels (Diamond et al., 1997).

1.2 Outcome in untreated PKU

The adverse outcome of untreated PKU is well-documented. Babies with PKU do not show any obvious abnormalities when they are born. However, their intelligence declines sharply over the first year of their life, and continues to decline at a slower rate until age three (Pietz, 1998). Knox (1972) notes that intelligence appears to remain

stable after this point, with adults with untreated PKU typically achieving IQ scores of significantly below 50. This may be considered to be in the "extremely low" range.

People with untreated PKU have been found to show high rates of epilepsy and progressive motor disturbances (Pietz, 1998), as well as increased levels of emotional and behavioural difficulties such as anxiety, depression, hyperactivity and aggression (e.g. Cowie, 1971; Wright & Tarjan, 1957; see Burgard, Armbruster, Schmidt & Rupp, 1994). Autopsy studies of people with untreated PKU have shown that this condition is associated with structural abnormalities of the brain, including low brain weight, reduced total white matter and disturbed myelination (see Knox, 1972; Pietz, 1998).

1.3 Treatment of PKU

The first successful treatment of a child with PKU was carried out by Bickel, Gerrard & Hickmans (1954; cited in Pietz, 1998). This treatment involved prescribing the child a diet that was very low in Phe (i.e. one in which natural protein was restricted). Guthrie & Susi (1963) later developed a simple method of identifying newborn infants with PKU on the basis of raised blood Phe levels. As a result of these advances, newborn screening programmes have been in place since the late 1960s, in order to identify all new cases of PKU in the U.K. This allows treatment of affected infants to begin within the first month of life (Guthrie, 1996).

Current approaches to the treatment of PKU involve two main elements. The first involves lowering blood Phe levels by severely restricting the amount of natural protein in the diet. The second involves using special Phe-free foods and dietary supplements to supply other essential amino acids, vitamins and minerals. The aim of treatment is to

keep blood Phe levels within a "safe" range, as both over- and under-treatment can be harmful. Patients are monitored through regular measurement of their blood Phe levels. This is usually achieved by having patients send in blood spots for laboratory testing.

It is generally agreed that treatment should begin as soon as possible in order to minimize the adverse effects of raised blood Phe levels on IQ (Legido et al., 1993, cited in Griffiths, Campbell & Robinson, 1998; Pietz, 1998). However, there is still controversy over the age at which dietary treatment should end, and the optimal blood Phe level to aim for during treatment (Medical Research Council, 1993a).

When dietary treatment for PKU was first introduced, the treatment was stopped when the patient reached 5 years of age. However, it later became apparent that this was not sufficient to prevent cognitive impairment (e.g. Koch, Azen, Friedman & Williamson, 1984; Holtzman, Kronmal, van Doorninck, Azen & Koch, 1986; Waisbren, Schnell & Levy, 1980). As a result, the age at which treatment is stopped has gradually increased to 8, 10, 12 and 16 years of age, and now there is a general "diet for life" policy in Britain. However, different policies have been adopted in different countries - for example, in France, dietary treatment is still stopped at age 5.

Policies have also changed with regard to the optimal blood Phe level to aim for during treatment. In the 1970s and 1980s, 600 μmol/l was widely accepted as the safe upper limit in early childhood (Griffiths, Tarrini & Robinson, 1997). Current U.K. guidelines now recommend upper limits of 360 μmol/l for young children, 480 μmol/l for school age children, and 700 μmol/l for patients above school age (although the difficulty of maintaining low blood Phe levels beyond childhood is recognized) (Medical Research

Council, 1993b). Again, however, different policies have been adopted in different countries – for example, until recently, higher blood Phe levels were considered to be acceptable in the United States (Diamond et al., 1997).

However, despite these continuing controversies, dietary treatments have transformed the outcome of PKU, and people with this condition are now able to lead relatively normal lives.

1.4 General intellectual function in treated PKU

A considerable amount of research has been carried out in order to try to assess outcome in treated PKU. Much of the early work in this area focused on outcome in terms of the IQ scores of treated individuals.

It has now been shown through a number of studies that children with early-treated PKU do not suffer the devastating cognitive impairments that are seen in untreated patients. Several studies have shown that children with treated PKU achieve IQ scores that are within the normal range (e.g. Holtzman, Kronmal, van Doorninck, Azen & Koch, 1986; Koch, Azen, Friedman & Williamson, 1982; Koch, Azen, Friedman & Williamson, 1984; Williamson, Koch, Azen & Chang, 1981). However, a number of studies have shown that patients' IQ scores often remain lower than those of their siblings and other family members, and lower than the mean of the general population (Koch, Azen, Friedman & Williamson, 1984; Medical Research Council, 1993a; Williamson, Koch, Azen & Chang, 1981). Hence several studies have shown that children with treated PKU often achieve IQ scores that are in the 80s or 90s – i.e. in the "low average" to "average" range (Berry, O'Grady, Perlmutter & Bofinger, 1979; Dobson et al., 1977;

Waisbren, Mahon, Schnell & Levy, 1987). A similar pattern appears to emerge in adults with treated PKU. For example, Pietz et al. (1998) found that their group of early-treated adults (age 17 to 33), most of whom were on-diet, achieved significantly lower IQ scores than a group of matched controls.

Several studies have also attempted to determine which treatment variables (such as age at diet initiation and termination, and quality of dietary control) are associated with more positive outcomes in treated PKU.

As previously noted, there is general consensus that early initiation of treatment is associated with higher IQ scores (Legido et al., 1993, cited in Griffiths, Campbell & Robinson, 1998; Pietz, 1998). However, the effect of the age at which diet is terminated has been more controversial. In an early review of 19 studies that had investigated the effects of diet termination in childhood, Waisbren et al. (1980) concluded that the evidence was equivocal. They reported that nine studies had found that ending dietary treatment in childhood resulted in significant reductions in IQ, whereas 10 other studies did not find any appreciable effect of diet termination. However, the authors noted that a number of methodological problems with these early studies (such as, for example, differences in the measures used or the lack of control groups) made it difficult to draw any firm conclusions from these data.

More satisfactory data has been obtained more recently from the U.S. National Collaborative Study of Treated PKU. This was a longitudinal study, which followed a group of children from birth to age 10. At age 6, the children in the study achieved a mean IQ score of 98 (Williamson, Koch, Azen & Chang, 1981). Higher IQ scores were associated with earlier initiation of treatment and better dietary control (Koch, Azen,

Friedman & Williamson, 1984; Williamson, Koch, Azen & Chang, 1981). The children were then randomly allocated to two groups, which would either continue or discontinue dietary treatment. When the children were re-tested two years later, it was found that the mean IQ score had not changed for either group, and that there was no significant difference in IQ between the groups (Koch, Azen, Friedman & Williamson, 1982). However, the group that had stopped treatment was found to have significantly lower IQ scores than their siblings (Koch, Azen, Friedman & Williamson, 1984). Furthermore, when the children were tested again at age 10, the best predictor of IQ was the age at which dietary treatment had stopped (Holtzman, Kronmal, van Doorninck, Azen & Koch, 1986). The results of several other studies have since supported the view that the age at which dietary treatment is stopped (Ris et al., 1994; Smith, Beasely & Ades, 1990; Schmidt, Mahle, Michel & Pietz, 1987) and the quality of dietary control during treatment (Schmidt et al., 1987; Smith, Beasely & Ades, 1990; Waisbren et al., 1987) affect IQ scores.

Hence, the evidence from studies of IQ in treated PKU suggest that IQ scores for this population are within the normal range, although they are perhaps lower than the mean for the general population. The majority of studies have also reported that higher IQ scores are associated with earlier initiation of treatment, better dietary control during treatment, and later discontinuation of treatment.

1.5 Specific cognitive functions in treated PKU

As IQ scores are a fairly insensitive measure of cognitive functioning, several later studies have looked at more specific cognitive processes in people with treated PKU, in

an attempt to specify which cognitive processes are impaired, and which intact in this population.

Waisbren, Brown, de Sonneville & Levy (1994) have reviewed the results of 21 such studies of neuropsychological function in treated PKU. They concluded that domains which have generally been found to be unaffected in this condition include speech, language, motor speed and some aspects of memory. Similarly, Welsh et al. (1990) concluded that language, perception, motor functions and memory have generally been found to be intact in people with treated PKU.

Nevertheless, people with treated PKU have been found to show impairments across a number of domains, including attention (Diamond et al., 1993; Pietz et al., 1993; Schmidt Rupp, Burgard & Pietz, 1992), perceptual-motor skills (e.g. Brunner, Jordan & Berry, 1983; Fischler et al., 1987; Koff, Boyle & Pueschel, 1977; Mims, McIntyre & Murray, 1983; Pennington, van Doorninck, McCabe & McCabe, 1985); visual-spatial problem solving (e.g. Davis, McIntyre, Murray & Mims, 1986; Faust, Libon & Pueschel, 1986; Fischler et al., 1987; Mims, McIntyre & Murray, 1981; 1983) and executive functions (Welsh et al., 1990) (see Waisbren et al., 1994; Welsh & Pennington, 2000).

However, more recently, Welsh and her colleagues (e.g. Welsh et al., 1990; Welsh & Pennington, 2000) have argued that the impairments that have been observed in these different domains may actually all reflect difficulties in a single domain - namely, the domain of executive functions. It is this hypothesis that will form the main focus of the present study.

1.6 Executive functions

1.6.1 Theoretical conceptualization

Executive functions are processes involved in the everyday control of thought and action. Burgess (1997) (citing Burgess & Cooper, 1996; Karnath, Wallesch & Zimmerman, 1991; Shallice, 1988 and Sirigu et al., 1995) suggests that there is general consensus that they consist of a set of processes whose main function is to aid adaptation to new situations. Furthermore, the executive system is considered to operate through "modulation and control of more fundamental or routine cognitive skills" (McCarthy & Warrington, 1990, p. 343, cited in Burgess, 1997).

Executive processes are, as yet, poorly understood. However, Rabbitt (1997) lists a set of behaviours that have generally been considered to be characteristic of executive, rather than non-executive, functions. First, executive functions are thought to be to necessary for the identification of goals in new situations. They are also thought to be required in order to select, carry out and monitor plans and to amend plans where necessary. Executive processes are also generally considered to be necessary for the initiation of new behaviours and the inhibition of contextually inappropriate responses. Rabbitt also points out that executive function has been held to be necessary for memory search (see Burgess, 1997) and for sustained attention (see Manly & Robertson, 1997).

In her work on executive function in PKU, Welsh (1996) has adopted the definition of executive function as "the ability to maintain an appropriate problem solving set for attainment of a future goal" (p. 1699). She and her colleagues have argued that

executive functions include planning, working memory, organized search, flexibility of thought and action and response inhibition (Welsh et al., 1990; Welsh, 1996; Welsh & Pennington, 2000).

1.6.2 Localization

Historically, the term "executive functions" has been used to describe the functions that are impaired in patients who have sustained damage to prefrontal (particularly dorsolateral) regions of the brain, and interconnected subcortical areas (Denckla, 1996). Indeed, Denckla suggests that the neuroanatomical description of executive functions has generally been more concrete than their theoretical description. There is still a reasonable degree of consensus that executive functions are primarily located in the frontal lobes, and the prefrontal cortex and its associated pathways in particular (e.g. Phillips, 1997; Norman & Shallice, 1986; although see Reitan & Wolfson, 1994, for alternative views). However, that is not to say that there is a one-to-one relationship between the prefrontal region and the areas of the brain that support performance on executive tasks. Indeed, the role of the prefrontal lobes is not limited to carrying out executive functions and, similarly, non-frontal areas of the brain are needed to support performance on executive tasks.

In recent years, our knowledge about the localization of cognitive functions in the brain has been extended through the use of functional imaging. Recent reviews of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies of the brain (Cabeza & Nyberg, 2000; Duncan & Owen, 2000) have suggested that mid-dorsolateral, dorsolateral, ventrolateral and anterior cingulate areas of the prefrontal cortex are crucial for the operation of executive functions, including working

memory, attentional control and inhibition. The extent to which these different regions support different functions remains to be established.

Further evidence on the localization of cognitive functions comes from studies of the effects of structural damage to the brain. Structural damage to the lateral prefrontal cortex is known to impair performance on tests of executive function in both humans and primates (see, for example, D'Esposito & Postle, 1999). Lesion studies have also suggested that the lateral prefrontal cortex may support different functions to orbital and medial regions of the prefrontal cortex (e.g. Bechara, Damasio, Tranel & Anderson, 1998; Dias, Robbins & Roberts, 1996; Rolls, Hornaz, Wade & McGrath, 1994). The latter regions may be more related to social and emotional behaviour, motivation and personality (Denckla, 1996).

1.7 Executive functions in PKU

1.7.1 The executive deficit hypothesis of PKU

As mentioned above, it has recently been argued that the cognitive profile of people with early-treated PKU is characterized by a disproportionate impairment of executive functions relative to other cognitive functions (Diamond et al., 1993; 1994; 1997; Welsh et al., 1990; Welsh & Pennington, 1988; 2000). It has been suggested that this selective impairment reflects dysfunction of the prefrontal cortex. More specifically, it has been argued that the functions of the prefrontal cortex may be impaired in PKU as a result of the adverse effect of raised blood Phe levels on the synthesis of catecholamines, particularly dopamine.

Welsh & Pennington (2000) have outlined three mechanisms whereby the synthesis of catecholamines may be disrupted in PKU. First, as noted above, the enzyme that converts Phe into tyrosine is inactive in people with PKU. As a result, levels of tyrosine are reduced in PKU. Tyrosine is necessary for the synthesis of dopamine and other catecholamines, and so reduced levels of tyrosine will result in reduced production of dopamine (see also Welsh, 1996). Second, although dietary treatment greatly reduces blood Phe levels in people with PKU, it does not, unfortunately, reduce them to normal levels (Diamond et al., 1997). Welsh & Pennington (2000) have suggested that the metabolites that result from these high Phe levels inhibit the enzymes that are necessary for the synthesis of catecholamines. Consequently, dopamine levels will be reduced even further. Finally, Phe, tyrosine and other large amino acids share a common transport system across the blood-brain barrier (e.g. Aragon, Gimenez & Valdivieso, 1982; Knudsen et al., 1995; Gardiner, 1990). High levels of Phe may therefore impede the transport of tyrosine and other amino acids to the brain. This may further reduce the levels of tyrosine available for dopamine synthesis in the brain.

Diamond and her colleagues (Diamond et al., 1997) have argued that, in untreated patients, or in patients who have discontinued dietary treatment, levels of Phe may be so high that there is a global disruption of dopamine metabolism in the brain. By contrast, in early and continuously treated PKU, Phe levels may only be moderately elevated and the reduction in the amount of tyrosine and other amino acids reaching the brain may be small. Diamond and her colleagues have pointed out that the dopamine neurons that project to prefrontal cortex have been shown to turn over dopamine faster than other neurons in the brain (e.g. Chiodo, Bannon, Grace, Roth & Bunney, 1984). This is likely to make them particularly sensitive to changes in the availability of tyrosine. As a result, the greatest effect of moderate reductions in

tyrosine (as are thought to occur in treated PKU) is likely to be on dopamine metabolism in the prefrontal cortex. Hence Diamond and her colleagues argue that, in treated PKU, moderately elevated Phe levels will result in dysfunction of the prefrontal cortex.

Finally, although high Phe levels also disrupt the synthesis of norepinephrine and seretonin (Butler, O'Flynn, Seifert & Howell, 1981; Guttler & Lou, 1986), the main theoretical focus has been on the effect of high Phe levels on the synthesis of dopamine. This is because norepinephrine and seretonin projections in the brain are more diffusely distributed than those of dopamine, and are thought to make much less specific contributions to cognition (Weglage et al., 1996).

1.7.2 Neuropsychological evidence in favour of the executive deficit hypothesis

The main approach to testing the executive deficit hypothesis has been to look at neuropsychological function in people with early and continuously treated PKU. Because continuous treatment of PKU has only recently been implemented, much of this work has been carried out with children.

Several studies which have looked at the cognitive abilities of young children with continuously treated PKU have found that these children show an apparently selective impairment on tests of executive function. For example, Welsh et al. (1990) found that their group of early and continuously treated children (age 4 to 5) were impaired relative to matched controls on a composite score representing performance across a variety of tests of executive function. By contrast, there was no difference between the groups on a test of recognition memory. A similar pattern of results has been reported from a 4-

year longitudinal study of children with early and continuously carried out by Diamond et al. (1997). This study included children ranging in age from infancy to school-age (age 6 months to 7 years), and compared their performance with that of three different control groups: siblings of the PKU group, matched controls and children from the general population. The authors found that children with blood Phe levels that were three to five times normal were impaired on certain tests of executive function. This difference remained even when IQ and various background variables were taken into account. By contrast, the children with PKU performed well on a range of control tasks, including tests of recognition memory, visuospatial processing, and rule learning. The authors noted that children whose blood Phe levels had remained below three times normal were found to perform as well as the control groups on all tasks. Diamond et al. argued that the executive tasks on which the children with blood Phe levels that were three to five times normal were impaired may have been those that are supported by the lateral prefrontal cortex, which may be particularly sensitive to reductions in dopamine.

Other studies have also found an apparently selective deficit for executive functions in older children. For example, Weglage et al. (1996) found that their group of early and continuously treated school-age children (age 8 to 13) were impaired on a task which is generally considered to be sensitive to executive deficits (the Stroop test) and on a task of sustained attention. (Welsh et al. (1990) have argued that sustained attention requires the executive functions of set maintenance and goal-directed activity, and hence may be considered to reflect prefrontal function (see also Manly & Robertson, 1997).) The children were not impaired on a control task that assessed short-term memory.

Because lifelong treatment for PKU has only been implemented fairly recently, very few studies have looked at neuropsychological outcome in adults with continuously treated PKU. In one study which did include adult participants, Stemerdink et al. (1999) found that their group of continuously treated participants (age 8-20) were impaired on tests of executive function relative to controls, even after the effects of IQ were taken into account. There was no difference between the groups on a set of control tasks. However, the participants in this study spanned a very large age range, and so it is difficult to ascertain neuropsychological outcome for adult subjects from this study.

Hence several studies have now found evidence of a selective deficit for executive functions in treated PKU. These deficits have typically been attributed to dysfunction of the lateral prefrontal cortex (e.g. Diamond et al., 1997).

1.7.3 Neuropsychological evidence against the executive deficit hypothesis

Several other studies have been carried out which undermine the view that people with early and continuously treated PKU necessarily show a selective impairment on neuropsychological tests of executive function.

For example, in a study of early and continuously treated school-age children with PKU (age 6 to 13), Mazzocco et al. (1994) did not find any evidence that this group showed an impairment on tests of executive function, or on a set of control measures. The fact that no executive deficits were observed in this study cannot be attributed to insensitivity of the measures used, as several of the measures were the same as those that had been used in the study reported by Welsh et al. (1990). Griffiths, Campbell & Robinson (1998) also found that their group of early and continuously treated children

(age 5 to 11) did not perform differently to matched controls on a continuous performance test of executive function. Given their failure to find executive deficits in school-age children, Mazzocco et al. suggested that the deficits which have been observed in young children may represent a developmental lag, which will eventually disappear with continued treatment. However, while this theory may account for the results obtained by Mazzocco et al. (1994) and Griffiths et al. (1998), it does not account for the selective deficit for executive functions shown by older children in the study by Weglage et al. (1996), described above.

As the results obtained with school-age children have been inconsistent, studies of early-treated adolescents and adults might be able to further our knowledge about developmental trends in treated PKU. However, as noted above, because consistent screening and treatment programmes have only been put into place fairly recently, there have been few studies of this type. In one study of early-treated adults (age 17 to 39), Smith, Klim, Mallozzi & Hanley (1996) found that the patient group was impaired relative to controls on both "frontal" and "posterior" tasks, although the authors argued that the most robust group differences were found on the former. The observation that patients were impaired on both types of task appears, at first sight, to be inconsistent with the executive deficit hypothesis of treated PKU. However, Smith et al. suggested that their failure to find the selective impairment on executive tasks that has been observed in children might reflect the fact that their subjects had been off-diet or on poorly controlled diets for 10-15 years. They suggested that the higher lifetime and concurrent blood Phe levels of their participants may have led to their showing more widespread cognitive deficits than those observed in young children. This position is consistent with the view expressed by Diamond et al. (1997), that patients who have

discontinued dietary treatment may have blood Phe levels that are sufficiently high to produce a global disruption of dopamine metabolism in the brain.

In another study of early-treated adults, Ris et al. (1994) found that their group of patients (age 18 and over) also showed impairments across a number of cognitive domains when their performance was compared to that of a group of sibling controls. Cognitive domains in which impairments were demonstrated included IQ, attention, problem-solving and visuo-constructive ability. However, once again, only 10 of the patients in the study had achieved continuous dietary adherence. Indeed, Ris et al. noted that the outcome for a subset of their patients who had maintained continuous dietary adherence appeared to be excellent. Unfortunately, the number of such patients who also had sibling controls was very small (N = 5), and so they were unable to carry out statistical analyses on the results for this group.

Hence while studies of children ranging in age from infancy to early school-age generally report that these children show a selective deficit on tests of executive function (e.g. Diamond et al., 1997; Welsh et al., 1990), findings on older participants are more equivocal. Some studies of older children have reported a selective deficit for executive functions similar to that observed in younger children (e.g. Weglage et al., 1996), but other studies have found no evidence of any impairments in this group (e.g. Griffiths, Campbell & Robinson, 1998; Mazzocco et al., 1994). The findings on developmental trends in early-treated PKU are therefore inconsistent. Studies of early-treated adolescents and adults might be able to provide further information about long-term outcome in PKU but, because lifelong treatment programmes have only been introduced fairly recently, few studies of this kind have been carried out. Most of the research that has been carried out with adults has involved participants who have

discontinued dietary adherence. The long-term outcome of early and continuously treated PKU therefore remains to be explored.

1.8 Influences on neuropsychological function in PKU

There has been a great deal of discussion in the literature as to the mechanisms through which the neuropsychological deficits seen in PKU are brought about. It has been suggested that these deficits may reflect both structural and biochemical changes in the brain. Furthermore, while the former are considered to be permanent, some authors have suggested that the latter may be, at least partially, reversible.

1.8.1 Structural influences on neuropsychological function in PKU

It has been argued that, in people with untreated PKU, high blood Phe levels result in disturbed myelination and synapse formation in the developing brain (Hommes, 1991). This view has been supported by animal studies, in which it has been shown that experimentally increased Phe levels produce disturbed myelination in rats (Huether, Kaus & Neuhoff, 1982). Diamond et al. (1997) suggest that the global impairments that are seen in untreated PKU may reflect these structural changes in the brain. Several authors have also suggested that structural changes of this kind are the main cause of irreversible cognitive impairments in treated PKU (e.g. Hommes, Eller & Taylor, 1982; Hommes and Matsuo, 1987. See Pietz et al., 1993).

1.8.2 Biochemical influences on neuropsychological function in PKU

Various studies have looked at the influence of both lifetime and concurrent blood Phe levels on cognitive function in PKU.

Several studies have found a relationship between lifetime blood Phe levels and cognitive function, particularly IQ (e.g. Pietz et al., 1993; Pietz et al., 1998). The effects of lifetime Phe levels may be mediated by the kind of structural changes outlined above, and hence may be permanent. There is also some evidence that high concurrent blood Phe levels may affect cognitive functioning, and executive functions in particular. It has been proposed that these effects are mediated by disturbed neurotransmitter synthesis, as described in Section 1.7.1 above (e.g. Diamond et al., 1997; Pietz et al., 1993). Furthermore, some authors have suggested that these effects may be, at least partially, reversible (e.g. Diamond et al., 1997).

For example, in their group of early and continuously treated children (aged 4 to 5), Welsh et al. (1990) found that performance on tests of executive function was strongly negatively correlated with concurrent blood Phe level, even after IQ was taken into account. There was not any significant relationship between performance on tests of executive function and lifetime blood Phe levels after IQ was taken into account. In contrast to the results of some other studies (e.g. Pietz et al., 1993; Pietz et al., 1998), these authors did not find any significant relationship between either concurrent or lifetime blood Phe levels and IQ. However, lifetime Phe levels were significantly correlated with memory functions when IQ was taken into account. Similarly, Diamond et al. (1997) found that, for their group of children with early and continuously treated PKU (age 6 months to 7 years), performance on the tasks that they argued are

supported by lateral prefrontal cortex was most strongly correlated with concurrent, rather than lifetime blood Phe levels. However, these authors found that IQ was also negatively correlated with Phe levels, and that this effect was again much stronger for concurrent, rather than lifetime Phe levels.

Other studies have obtained similar results with older groups of participants. For example, Weglage et al (1996) found significant negative correlations between concurrent blood Phe levels and performance on tests of executive function and sustained attention in their group of older children (age 8 to 13). Schmidt, Burgard & Rupp (1996) divided their group of early-treated children (age 8 to 9) into two groups based on their lifetime and concurrent blood Phe levels. They found that low concurrent Phe levels were associated with significantly better performance on a task of sustained attention if lifetime levels were low, but not if they were high. Finally, in their study of a group of early-treated adults (age 17 to 33; most of whom were on-diet), Pietz et al. (1998) found that performance on an attention task was influenced by both concurrent Phe levels and Phe levels from age 12 to adulthood.

However, not all studies have observed significant associations between blood Phe levels and cognitive abilities. For example, Griffiths, Campbell & Robinson (1998) found that for their group of early and continuously treated school-age children (age 5 to 11), performance on a continuous performance test of executive function was not associated with either historical or current blood Phe levels. Similarly, Griffiths, Tarrini & Robinson (1997) did not find any clear relationship between either current or historical blood Phe levels and neuropsychological measures in a slightly older group of early and continuously treated children (age 10 to 13). Stemerdink et al. (1999) also failed to find

any clear relationship between blood Phe levels and performance on executive tasks in their group of continuously treated older participants (age 8-20).

A possible explanation for the different patterns of results that have been obtained has been proposed by Griffiths and her colleagues (Griffiths, Campbell & Robinson, 1998). These authors have suggested that the different patterns of results obtained in their own study and the study by Weglage et al. (1996) could have arisen because the children in the latter study had slightly higher historical and significantly higher concurrent Phe levels. The mean concurrent Phe level for the children in the study by Griffiths, Campbell & Robinson (1998) was 388 μmol/l, as compared to 583 μmol/l in the study by Weglage et al. This argument could also account for the fact that significant associations were found between concurrent Phe levels and performance on executive tasks in the studies carried out by Welsh et al. (1990) (mean concurrent Phe level = 564 μmol/l) and Pietz et al. (1998) (mean concurrent Phe level = 1085 μmol/l). However, it is not clear that this argument could account for the results obtained by Diamond et al. (1997), as Phe levels in this study were rather lower (mean Phe = 388 μmol/l for infants, 477 μmol/l for toddlers and 445 μmol/l for young children).

There is not, therefore, any current consensus as to the relationship between concurrent blood Phe levels and cognitive performance in treated PKU. However, in order to investigate the relationship between these variables further, several studies have looked at the effects of experimental manipulation of blood Phe levels in people with PKU. Several of these studies have found that experimental manipulation of blood Phe levels does indeed produce corresponding changes in performance on neuropsychological tasks.

For example, Krause et al. (1985) looked at the effect of experimental changes in blood Phe levels on a group of PKU patients (age 6 to 24, and mixed in terms of their adherence to dietary treatment) using a double crossover design. They reported that, when Phe levels were elevated, performance on tests of higher integrative functions deteriorated, whereas lower integrative functions were unaffected. Similarly, Pietz et al. (1993) studied five adult patients under conditions of high and low blood Phe levels, and found that performance on neuropsychological tasks of sustained attention and divided attention was impaired when Phe levels were high. In another study, Schmidt et al. (1994; see also Schmidt et al., 1996) studied a group of early-treated adults (age 17 to 24) who had high blood Phe levels, and who showed impairments on tasks of sustained attention and reaction time. These authors found that lowering the participants' Phe levels by returning to them to a strict diet for 4-5 weeks improved their performance on these tasks, although their performance was still not as good as that of healthy controls.

However, results are again mixed. For example, Realmuto et al. (1986) found that raising blood Phe levels experimentally in a group of children and adolescents with early-treated PKU who were off-diet (age 9 to 20) did not impair performance on tasks which required sustained attention or working memory and inhibition. Similarly, Clarke, Gates, Hogan, Barret & McDonald (1987) found that, in their group of early-treated adolescents (age 11 to 18) who were off-diet, lowering blood Phe levels resulted in improved choice reaction times, but did not affect performance on three other tests of executive function (Fluency, the Stroop test and Trail Making).

Several of the studies that have failed to find an effect of experimental manipulation of blood Phe levels on cognitive performance have involved participants who were off-diet.

As Welsh & Pennington (2000) have argued, it is possible that, in these participants, temporary changes in Phe levels are not enough to override the effect of permanent brain damage. However, this argument does not account for the results obtained by Griffiths, Ward, Harvie & Cockburn (1998) in their study of a group of continuously treated children (age 10 to 16). These authors found that raising blood Phe levels experimentally for three months did not produce any effect on performance on a neuropsychological test battery, including tests of verbal and spatial memory, attention and fine motor coordination.

Another possible explanation for the inconsistent relationships that have been observed between blood Phe levels and cognitive performance has been suggested recently by results reported from a 15-year follow up of people who took part in the U.S. National Collaborative Study of Treated PKU (Koch et al., 2000). These authors assessed participants' brain Phe levels using Magnetic Resonance Spectroscopy (MRS), and compared them with simultaneously measured blood Phe levels. The results suggested that blood Phe levels do not, in fact, predict brain Phe levels. Future MRS studies may help to clarify whether brain Phe levels are able to predict patients' performance on neuropsychological tests more reliably than blood Phe levels.

Overall, therefore, studies of the relationship between concurrent blood Phe levels and cognitive performance have provided some evidence in favour of the executive deficit hypothesis of treated PKU. As would be predicted by the executive deficit hypothesis, a number of studies have found a significant negative correlation between concurrent Phe levels and performance on tasks of executive function in people with treated PKU (Diamond et al., 1997; Schmidt et al., 1996; Welsh et al., 1990). However, there is, as yet, no consensus on this issue, as some studies have failed to find any significant

relationship between these variables (Griffiths, Campbell & Robinson, 1998; Griffiths, Ward, Harvie & Cockburn, 1998). These inconsistent patterns of results may reflect low correlations between blood Phe levels and brain Phe levels (Koch et al., 2000). Future research studies may clarify whether brain Phe levels correlate more reliably with cognitive performance.

1.9 Neurological outcome in treated PKU

It is well established that people with untreated or late-treated PKU show neurological impairments. Subtle neurological signs (such as brisk reflexes and tremor) are also quite common in early-treated patients who are off-diet (Pietz, 1998). More worryingly, there have been reports of cases of treated patients who have suffered serious late-onset neurological deterioration after they have come off diet (e.g. Vissana, Butler, Williams & Roongta, 1989; Thompson et al., 1990). However, this type of deterioration has usually occurred in patients who started treatment late, had poor dietary control in childhood or showed signs of neurological problems prior to the deterioration (see Pietz, 1998).

The possibility that there may be some subtle neuropathology in people with PKU even while they remain on diet has been investigated through studies of fine motor skills in this population. Several of these studies have found these skills to be impaired in children with treated PKU (e.g. Weglage et al., 1984; Weglage, Pietsch, Funders, Koch & Ullrich, 1995). Similarly, Pietz et al. (1998) found evidence of increased tremor and reduced fine motor abilities in a group of adults with early-treated PKU (age 17 to 33), most of whom were on-diet. Findings such as these support the view that there may be some subtle neuropathology even in continuously treated PKU.

Other studies have investigated the possibility of neuropathology in treated PKU by looking at electroencephalogram (EEG) patterns in this population. Several studies have shown that abnormal EEG patterns are very common in people with untreated PKU (e.g. Lutcke, 1971; Rolle-Daya, Pueschel & Lombroso, 1975; see Pietz et al., 1993). However, results for people with early-treated PKU are more equivocal. While some studies have shown increased numbers of abnormalities in this population (e.g. Gross, Berlow, Schuett, & Fariello, 1981; Korinthenberg, Ullrich & Fullenkemper, 1988; Rolle-Daya et al., 1975; see Pietz et al., 1993), others have not (e.g. Blascovic et al., 1988). Pietz et al. (1993) suggest that this may be a result of differences in the samples used (e.g. in terms of age, age at diet onset and quality of dietary control) and the number and frequency of EEG recordings.

Findings on the relationship between blood Phe levels and EEG patterns are also equivocal. Some studies have found that abnormalities in EEG patterns are related to Phe levels (e.g. Donker, Reits, Van Sprang, Storm van Leewn & Wadman, 1979; Degiorgio, Antonozzi, Del Castello & Loizzo, 1982), while others have not found any significant relationship between these variables (Gross et al., 1981; Pietz et al., 1993; Rolle-Daya et al., 1975). It is therefore difficult to draw any clear conclusions at the present time as to whether people with treated PKU show increased levels of EEG abnormalities, and whether their EEG patterns are influenced by concurrent blood Phe levels.

Another approach to looking at the neurophysiology of people with treated PKU has been to look at visual and somatosensory evoked potentials (EPs) in this population. EPs are similar to event-related potentials (ERPs), except that the participant is passive (see Welsh & Pennington, 2000). Several studies have found increased visual EP

latencies in people with treated PKU (e.g. McCombe et al., 1992; Pueschel, Fogelson-Doyle, Kammerer & Matsumiya, 1983; both cited in Welsh & Pennington, 2000; Cleary et al., 1994; Leuzzi et al., 1998; Ludolph et al., 1992; Pietz et al., 1996). However, there is no consensus as to whether increases in latency are correlated with age of diet initiation or biochemical control (Pietz, 1998). Auditory EPs are usually found to be normal (Pietz, 1998), and there is equivocal evidence as to whether patients show abnormalities in somatosensory EPs (Cleary et al., 1994; Ludolph et al., 1992). However, as Welsh & Pennington point out, as EPs are thought to be related to primary sensory pathways rather than higher cognitive functions, the abnormalities that have been observed in visual EPs do not appear to be consistent with the executive deficit hypothesis of treated PKU.

Overall, therefore, while there is some evidence from studies of fine motor skills, EEG patterns and visual EPs in people with continuously treated PKU that there may be some subtle neuropathology in this population, there is, as yet, little evidence from these studies that specifically supports the executive deficit hypothesis of treated PKU. As Welsh & Pennington (2000) point out, methods that allow more specific links to be made between neurophysiological events and particular cognitive processes – such as, for example, ERP studies – may be more informative in this regard.

1.10 Brain imaging data in treated PKU

More recently, brain imaging studies have been used to try to further specify the mechanisms that underlie the cognitive impairments seen in treated PKU.

In their review of magnetic resonance imaging (MRI) studies of people with treated PKU, Welsh & Pennington (2000) conclude that several of these studies have now found evidence of abnormalities in cerebral white matter, as well as evidence of defective myelination in the brain. A number of studies have found that these changes are particularly pronounced in posterior periventricular areas (e.g. Bick et al., 1993; Ullrich et al., 1994; Weglage, Pietsch, Funders, Koch & Ullrich, 1995). However, in more severe cases, frontal and subcortical white matter may also affected (e.g. Bick et al., 1993; Pietz, 1998).

Several studies have failed to find any consistent relationship between MRI findings and patients' treatment histories (such as their age at diet initiation and termination and the quality of their dietary control during treatment) (e.g. Bick et al., 1993; Pearson, Gean-Marton, Levy & Davis, 1990). Instead, MRI abnormalities seem to be related to current blood Phe levels (Bick et al., 1993; Cleary et al., 1994; Thompson et al., 1993). Furthermore, MRI abnormalities may be reduced by a return to strict dietary control (Bick et al., 1993; Cleary et al., 1995). Hence the white matter changes seen in treated PKU may represent reversible structural changes in myelin rather than permanent demyelination (Bick et al., 1993).

Overall, the evidence from brain imaging studies does not appear to be particularly supportive of the executive deficit hypothesis of PKU, as MRI abnormalities typically extend to the frontal cortex only in severe cases. However, as Welsh & Pennington (2000) point out, no correlations have yet been observed between MRI abnormalities and neurological, electrophysiological and neuropsychological measures (Bick et al., 1993; Cleary et al., 1994; Pietz, 1998; Thompson et al., 1993). Hence the changes that can currently be seen with MRI scans may not be those responsible for the

neuropsychological deficits that are seen in treated PKU. A limitation of MRI scans is that they can show only structural changes in the brain. However, more advanced methods, such as MRS, which can be used to scan for chemical compounds (such as Phe) in the brain, may be used in the future to advance our knowledge about the relationship between elevated Phe levels and performance on neuropsychological tasks.

1.11 Psychiatric symptomatology in treated PKU

Finally, Welsh & Pennington (2000) have also argued that the executive deficit hypothesis of PKU is supported by findings on the emotional and behavioural characteristics of people with treated PKU.

Indeed, the findings of several studies of emotional and behavioural outcome in children with early-treated PKU (both on and off-diet) could be argued to be consistent with the hypothesis that these children show impairments of executive functioning. Various studies have reported that such children show higher levels of behaviour problems than controls. These include symptoms such as reduced persistence (Schor, 1983), poor impulse control (Fisch, Sines & Chang, 1981), irritability (Michals, Dominik, Scuett, Brown & Matalon, 1985) and attention deficits and hyperactivity (Michals et al., 1985; Realmuto et al., 1986; Smith, Beasley, Wolff & Ades, 1988).

However, studies which have looked at emotional and behavioural outcome in relation to metabolic control have generally not found any significant relationship between these variables. For example, Griffiths, Tarrini & Robinson (1997) found no clear relationship between either concurrent or historical blood Phe levels and personality measures in

their group of early and continuously treated children (age 10 to 13). Similarly, Weglage et al. (1995a, cited in Griffiths, Campbell & Robinson, 1998) did not find any relationship between preschool blood Phe levels and behavioural adjustment in their group of treated children (age 10). The lack of a significant association with metabolic control undermines an explanation of the emotional and behavioural difficulties that have been observed in children with early-treated PKU in terms of alterations in neurotransmitter levels and associated impairments of executive functioning.

An alternative possibility is that the emotional and behavioural disturbances shown by children with treated PKU are a result of the stress involved in coping with a chronic disorder rather a direct result of altered neurotransmitter levels. This is the view favoured by Burgard et al. (1994). These authors assessed a group of early-treated adolescents who were taking part in the German collaborative study of PKU (N = 60, age = 13) using a standardized psychiatric interview. The authors reported that the PKU sample showed twice the rate of moderate psychiatric disturbances compared to age-matched controls. However, no PKU-specific diagnoses were identified, and there was no association between psychiatric disturbance and lifetime blood Phe levels. Hence the authors argued that the results were not consistent with the view that the mental health difficulties were a direct effect of raised Phe levels.

There have been fewer studies of emotional and behavioural outcome in adults with treated PKU. However, in one such study, Waisbren & Zaff (1994) looked at the profiles of women with treated PKU on the Minnesota Multiphasic Personality Inventory (MMPI). They suggested that these women showed a tendency towards higher scores on scales related to thought disorder and mood disturbance. The authors suggested that this type of profile could be the result of changes in catecholamine levels.

In another study of psychosocial outcome in adults with early-treated PKU (both on- and off-diet), Ris et al. (1997) found that, on most measures, patients were no different from sibling controls. However, on the Symptom Checklist-90-Revised (SCL-90-R), the patient group was more likely to show significant morbidity. This result was found to be produced by 20% of the PKU group. These authors found that psychiatric morbidity was not related to dietary control, but was related to measures of cognitive functioning. The highest correlation was with performance on the Wisconsin Card Sort Test (a test widely used as a measure of executive function). Hence the authors suggested that people with PKU might be at greater risk of mental health difficulties as a result of specific cognitive difficulties, and particularly problems with self-regulation, planning and the ability to deal flexibly with demands.

Overall, therefore, several studies have found that both children and adults with treated PKU are at increased risk of emotional and behavioural problems. No direct relationship between psychiatric morbidity and metabolic control has been demonstrated which, to some extent, undermines the hypothesis that these difficulties are the result of altered neurotransmitter levels. (Although, as noted above, there may be low correlations between blood Phe levels and brain Phe levels.) However, the relationship between psychiatric morbidity and cognitive functioning observed by Ris et al. (1997) leaves open the possibility that mental health difficulties in this population may be mediated by particular cognitive deficits.

1.12 Rationale for the current study

Modern screening and treatment programmes have transformed the lives of people with PKU. However, the long-term outcome of treated PKU is still being explored.

According to the executive deficit hypothesis of treated PKU (e.g. Diamond et al., 1997; Welsh et al., 1990), this condition is characterized by a selective impairment of executive functions, reflecting dysfunction of the prefrontal cortex. Several studies of young children with early-treated PKU have now found evidence in support of this hypothesis (e.g. Diamond et al., 1993; 1997; Welsh et al., 1990). However, as noted above, it is not clear whether this pattern remains consistent over development. Some studies of older children have found that they show a selective deficit for executive functions similar to that observed in young children (Weglage et al., 1995b; 1996), whereas others have found no evidence that these children show any cognitive deficits (Griffiths, Campbell & Robinson; 1998; Mazzocco et al., 1994). Indeed, Welsh & Pennington (2000) have argued that the issue of whether the neuropsychological sequelae of treated PKU change with development remains one of the major research questions in this area.

Studies of early-treated adolescents and adults might be able to further our knowledge about the long-term outcome of treated PKU but, because consistent screening and treatment programmes have only been put into place fairly recently, there have been few studies of this type. Again, as noted above, the results of the studies which have been carried out are mixed. Some studies have found evidence that early-treated adolescents and adults show a selective deficit for executive functions, similar to that which has been observed in young children (Stemerdink et al., 1999). Others have found evidence of more widespread deficits (Ris et al., 1994; Smith et al., 1996). However, methodological problems with these studies make these results difficult to interpret. For example, the sample studied by Stemerdink et al. (1999) spanned a very wide age band (age 8 to 20), making it difficult to assess whether children and adults showed different cognitive profiles. Studies which have found evidence of more

widespread cognitive deficits (e.g. Ris et al., 1994; Smith et al., 1996) have been carried out with adults who have discontinued dietary treatment. The long-term outcome of early and continuously treated PKU therefore remains to be explored.

There are several possible approaches to the question of whether the cognitive impairments observed in children with treated PKU represent a permanent deficit or whether they are better viewed within a developmental lag model (Welsh & Pennington, 2000). One approach would be to carry out a cross-sectional study, comparing the cognitive profiles of early-treated individuals of different ages. However, Welsh & Pennington note that a problem with this approach is that patients' age is confounded with changes in the medical treatment of PKU. As a result, it would not be clear from this type of study which of these factors was responsible for any observed difference between the cognitive profiles of children and adults. Welsh & Pennington therefore suggest two alternative approaches to this research question. The first is to look at developmental trends using longitudinal studies, while the second is to look at samples which are more homogeneous in terms of age (so that, for example, children and adults are not mixed together in the same sample). The present study takes the second of these approaches, looking at the neuropsychological profile of a group of adults with early and continuously treated PKU.

In order to investigate outcome in adults with continuously treated PKU it would, ideally, be possible to compare their performance directly with that of a group of similarly aged patients who were off diet. However, because treatment advice has changed over time, people who were advised to remain on diet into adulthood will be a different age to those who were advised to come off diet before adulthood. Furthermore, amongst those who were advised to remain on diet, there may be systematic differences

between those people who did actually stay on diet and those who elected to come off diet against medical advice. This study therefore compares a group of adults who remained on diet with a group of matched healthy controls without PKU.

The main aim of the study is to find out whether adults with early and continuously treated PKU show a selective deficit for executive functions, as has been observed in young children. The study involves comparing the performance of patients and controls on a battery of neuropsychological tests. The test battery includes measures of executive function considered to be sensitive to dysfunction of the prefrontal cortex, as well as tests that are thought to make fewer demands on executive processes. Questionnaires are also used to assess the extent to which participants experience problems associated with executive deficits in everyday life, and the extent to which they experience any emotional difficulties.

Following several previous studies (e.g. Burgard et al., 1997; Clarke et al., 1987; Mazzocco et al., 1994; Weglage et al., 1995b; 1996; Welsh et al., 1990; Smith et al., 1996), the patient group and the control group will be matched on age, sex and IQ. Matching for IQ means that the results of this study cannot be used to assess whether the PKU participants have achieved the level of cognitive abilities that they would have achieved if they had not had PKU. However, this design does allow for a stronger test of the executive deficit hypothesis of PKU. This is because any deficit shown by the PKU group on the tests of executive function cannot be attributed to lower general intelligence in this group. Furthermore, it has been argued that it is particularly important to take IQ into account when assessing performance on tests of executive function. This is because a person's IQ will affect how difficult a particular task is for

them, and hence how sensitive that task will be to executive function for that individual (Denckla, 1996).

Finally, as both lifetime and concurrent blood Phe levels have been shown to affect cognitive performance in PKU it would, ideally, be possible to include measures of both of these variables in this study. Unfortunately, however, lifetime Phe levels were not available, and so measures of concurrent and longer-term Phe levels (covering the two years preceding cognitive testing) will be included in the study. The relationship between these variables and participants' performance on the neuropsychological tasks will then be assessed.

1.13 Selection of neuropsychological measures

As noted above, according to the executive deficit hypothesis, the cognitive deficits that have been observed in treated PKU are caused by dysfunction of the lateral prefrontal cortex. A set of tests was therefore chosen for this study that tapped cognitive functions that are thought to be supported by different regions of the prefrontal cortex. More specifically, tests were chosen to assess the executive functions of working memory, response initiation/suppression and attention. These functions were chosen as they are thought to be supported by dorsolateral prefrontal cortex, ventrolateral prefrontal cortex and the anterior cingulate respectively. Ideally, it would be possible to compare performance on these tasks with performance on tasks that do not make any demands on prefrontal cortex. However, identifying tasks that do not draw on prefrontal cortex is difficult, as functional imaging studies have shown that almost all high-level tasks activate prefrontal cortex to some extent (Cabeza & Nyberg, 2000). A set of memory tests was therefore selected for comparison with the executive tests in this

study, on the basis that the former are usually considered to be less sensitive to frontal lesions (e.g. Janowsky, Shimamura, Kritchevsky & Squire, 1989). Empirical data on the functional localization of the cognitive processes that are thought to support performance on each of these tests are outlined below, while the tests themselves are described more fully in the Method section (Section 2.4).

Of course, it is important to note that performance on these tests is not supported exclusively by the brain regions with which they are associated here. Indeed, performance on each of these tests is likely to require activity across a number of different brain regions. However, a comprehensive review of the overlapping demands (both functional and anatomical) of the different tests is beyond the scope of this study. The tests are therefore categorized here on the basis of the *relative* contribution of different brain regions to their performance.

1.13.1 Measures of executive functions

1.13.1.1 Working memory

The term "working memory" has been used to describe a cognitive system which is used for the temporary storage and manipulation of information (Baddeley, 1992). It has been argued that working memory tasks involve both executive components (supported by frontal cortex) and mnemonic components (supported by medial temporal lobe structures) (Owen et al., 1996). However, while there is good evidence from lesion studies and functional neuroimaging studies that the lateral frontal cortex plays a crucial role in working memory (Cabeza & Nyberg, 2000; Owen, Lee & Williams, 2000), there is more controversy over how working memory processes within this region may be fractionated. One view that has been proposed is that working memory functions are

organized according to the nature of information being processed. Hence it has been argued that dorsolateral regions support working memory for spatial information, and ventrolateral regions support working memory for non-spatial information (e.g. Goldman-Rakic, 1995). However, while some evidence has been obtained in favour of this hypothesis, there has, overall, been little support for this view (see Owen, 1997, for a review of fMRI studies in this area). Instead, it seems that the available empirical evidence favours the view, proposed by Petrides (1994), that working memory functions are organized according to the *type* of processing required. According to this theory, basic memory functions are supported by the parietal and temporal cortices. Second order processes (such as making comparisons between stimuli, and initiating basic encoding and retrieval strategies) are supported by ventrolateral frontal cortex. Finally, third order processes (involving the active manipulation and monitoring of information) are supported by mid-dorsolateral frontal cortex (see Owen et al., 2000; Petrides, 1994).

For this study, two tests involving working memory were chosen, on which performance is thought to be supported by dorsolateral frontal cortex. These were The Brixton Test (Burgess & Shallice, 1997) and The Self-Ordered Pointing task (Petrides & Milner, 1982).

The Brixton Test (Burgess & Shallice, 1997) is a test involving rule detection and rule following. The participant must predict the location of a target, by detecting various rules that come and go without warning. Burgess & Shallice (1997) have argued that this test shares processing resources with other rule-detection tasks, such as the Wisconsin Card Sorting Test (WCST; Milner, 1963). The WCST is known to be difficult for people with frontal lesions (Anderson, Damasio, Jones & Tranel, 1991; Strauss,

Hunter & Wada, 1993; Stuss, Ekes & Foster, 1992; see Burgess & Shallice, 1997), and people with dorsolateral lesions in particular (Milner, 1963). It has been suggested that these difficulties reflect dysfunction of working memory systems supported by the prefrontal cortex (e.g. Goldman-Rakic, 1991). In addition, while functional imaging studies have shown that a number of brain regions are involved in performance of the WCST (Cabeza & Nyberg, 2000), the performance of rule-detection tasks has been particularly associated with activation of the dorsolateral prefrontal cortex (e.g. Rogers et al., 2000). Burgess & Shallice (1997) have argued that the Brixton Test is a purer rule-detection task than the WCST, and it was chosen over the WCST in this study because of its greater ease and speed of administration.

The Self-Ordered Pointing task (SOP; Petrides & Milner, 1982) is a test in which the participant must point to each of a series of stimuli in turn, avoiding repetition. Petrides (1991) argues that this task demands on-line monitoring, and hence requires working memory. Petrides & Milner (1982) found that patients with frontal lesions were impaired on both verbal and non-verbal versions of this task, whereas patients with temporal lesions that did not involve extensive damage to the hippocampus did not show any deficits. It has been suggested that the deficits shown by people with frontal lesions on this task may reflect difficulties in organizing and monitoring sequences of responses (Owen et al., 1996; Petrides & Milner, 1982). Petrides, Alivisatos, Meyer & Evans (1993) have reported evidence from a PET study to show that performance on verbal SOP (as used in the present study) is associated with strong bilateral activation of the mid-dorsolateral frontal cortex (see also Owen et al., 1998).

1.13.1.2 Response initiation and suppression

As Burgess & Shallice (1997) point out, a number of studies have found evidence of impaired response initiation and response suppression in people with frontal lobe dysfunction (e.g. Duncan, Johnson, Swales & Freer, 1997; Stuss & Benson, 1984). In this study, two tests of response initiation and suppression were chosen as tests on which performance is thought to be supported by the ventrolateral frontal cortex. These tests were Letter Fluency and The Hayling Test (Burgess & Shallice, 1997).

In Letter Fluency tasks, participants are typically asked to give as many words as they can think of that begin with a certain letter, within a given time limit. Perrett (1974) has argued that Letter Fluency tasks require both response initiation and suppression, as participants must both retrieve appropriate words, and suppress inappropriate words. Patients with lateral prefrontal lesions have been shown to be impaired on letter fluency tasks (Baldo & Shimamura, 1998). In addition, several fMRI studies have now found evidence that Letter Fluency produces increased activity of the left inferior frontal gyrus (which forms part of the ventrolateral prefrontal cortex) (e.g. Paulesu et al., 1997; Phelps, Hyder, Blamire & Shulman, 1997).

The Hayling Test (Burgess & Shallice, 1997) consists of two sentence completion tasks, which provide measures of response initiation and response suppression. Burgess & Shallice (1997) found that patients with frontal lesions performed more poorly than controls on both tasks, whereas patients with damage to more posterior areas of the brain did not show any deficits. Nathaniel-James, Fletcher & Frith (1997) have reported evidence from a PET study of healthy participants that suggests that both the response initiation and response suppression tasks produce increased activation in the left inferior frontal gyrus, left frontal operculum, and right anterior cingulate.

1.13.1.3 Attention

Posner & Petersen (1990) have proposed a model of attention that incorporates three separate subsystems for attention and arousal. First, they suggest that a posterior attentional system is involved in orienting attention in space. Second, they suggest that an anterior attentional system is involved in selective attention. Finally, they propose that an arousal system, supported by the reticular system, supports sustained attention. Measures assessing the latter two subsystems were chosen for this study.

Selective attention involves attending to one stimulus rather than another (Coull, 1998). Evidence from PET studies suggests that tasks requiring selective attention produce increased activation of the anterior cingulate and adjacent frontal areas (Bench et al., 1993; Carter, Mintun & Cohen, 1995; Pardo, Pardo, Janer & Raichle, 1990). For example, Coull, Frackowiak & Frith (1998) observed increased activation of right dorsolateral prefrontal cortex and the anterior cingulate during a task in which participants were asked to respond selectively to serially presented targets. Sustained attention refers to the ability to maintain attention to stimuli over a prolonged period of time (Coull, 1998). Wilkins et al. (1987) have reported that people with right frontal lesions show particular difficulty on tests of sustained attention. In addition, several PET studies have found evidence of increased right dorsolateral prefrontal activation during sustained attention tasks (e.g. Cohen et al., 1988; Pardo, Fox & Raichle, 1991). Two measures of attention were used in the present study. These were Telephone Search and Telephone Search with Counting (Robertson, Ward, Ridgeway & Nimmo-Smith, 1994).

Both Telephone Search and Telephone Search with Counting are taken from the Test of Everyday Attention (Robertson et al., 1994). In Telephone Search, participants must

search through a "telephone directory" looking for particular symbols. In Telephone Search with Counting, they must search for symbols as before, but must also count a series of tones at the same time. In an analysis of data from healthy participants, Robertson et al. (1994) found that Telephone Search loaded on a "selective attention" factor, while Telephone Search with Counting loaded on a "sustained attention" factor.

1.13.2 Measures of recall and recognition memory

As noted above, it is difficult to identify tasks that do not make any demands on prefrontal cortex for comparison with the executive measures, as functional imaging studies have now shown that almost all high-level tasks produce some activation of this region (Cabeza & Nyberg, 2000). Hence, while memory functions have typically been associated with more posterior regions of the brain (e.g. Tranel & Damasio, 1995), functional imaging studies have now shown that both anterior and posterior brain regions contribute to performance on memory tests (Cabeza & Nyberg, 2000). However, lesion studies have frequently reported finding performance on memory tests to be relatively immune from the effects of frontal lesions (Kesner, Hopkins & Fineman, 1994; Milner et al., 1991; Janowsky, Shimamura, Kritchevsky & Squire, 1989). This may be especially true for tests of recognition memory. Hence, in a meta-analysis of studies of memory function in patients with frontal lesions, Wheeler, Stuss & Tulving (1995) found that less than half of the studies (44%) had reported finding statistically significant memory impairments in this population. The percentage was also much lower for studies that had tested recognition memory (8%) than for studies that had tested free recall (80%). There is also some evidence from functional imaging studies that tests of recognition memory may make fewer demands on frontal regions than tests of free recall (e.g. Schacter et al., 1996). These differences between the results

obtained with tests of free recall and tests of recognition memory are consistent with the view that the frontal lobes may make a strategic contribution to memory encoding and retrieval (Gershberg & Shimamura, 1995; Incisa della Rocchetta & Milner, 1993).

Overall therefore, there seems to be some evidence that memory tests, and tests of recognition memory in particular, may be relatively immune from the effects of frontal lesions. For this reason, as in several other studies of cognitive functions in PKU (e.g. Griffiths et al., 1997; Mazzocco et al., 1994; Ris et al., 1994; Smith et al., 1996; Stemerdink et al., 1999; Welsh et al., 1990), a set of measures of memory was selected for comparison with the measures of executive function in this study.

Because of the hypothesized differences between tests of free recall and recognition memory, in terms of the extent to which they place demands on the prefrontal cortex, tests which yield measures of both free recall and recognition were chosen. As measures of free recall are likely to make at least some executive demands, it is possible that these measures might be sensitive to dysfunction of the lateral prefrontal cortex in treated PKU. However, as recognition memory is though to make fewer demands on processes supported by the prefrontal cortex, it seems likely that these measures will not be affected in treated PKU. Finally, as processes supporting memory for visual and verbal material have been shown to be more strongly associated with the right and left hemispheres, respectively (Cabeza & Nyberg, 2000), measures of memory for both verbal and non-verbal material were selected.

The two tests that were chosen for this study were The Rey Auditory Verbal Learning Test (Rey, 1964; Taylor, 1959) and The Complex Figure Test (Rey, 1941; Meyers & Meyers, 1995; Osterrieth, 1944). The Rey Auditory Verbal Learning Test was used to

provide measures of recall and recognition memory for verbal material, while The Complex Figure Test was used to provide measures of recall and recognition memory for visual material.

1.13 Clinical importance of the current study

A greater knowledge of the cognitive status of adults with early and continuously treated PKU will help to clarify their potential with optimal treatment. Further information on the characteristics of any cognitive impairments that are seen in this population (such as whether they are specific to executive functions, which are thought to be supported by the prefrontal cortex) may also help to clarify the mechanisms underlying these impairments. This may in turn help to inform future developments in terms of treatment options.

Further clarification of the long-term outcome of continuously treated PKU is particularly important given that the dietary treatment is so demanding for the person with PKU. As Thompson et al. (1990) note, the diet is difficult to follow, expensive, and can contribute to nutritional problems if followed badly. The treatment is also very expensive for the NHS, costing around £10 000 per person per year. This means that to maintain a person with PKU on diet beyond adolescence costs around £500 000. It is therefore important that treatment decisions can be informed by data on long-term outcome.

1.14 Hypotheses

The hypotheses to be tested in this study may be summarized as follows:

(1) Individuals with PKU will show a deficit relative to controls on tasks that make greater demands on executive functions.

(2) Better performance on tasks that make greater demands on executive functions will be associated with lower concurrent blood Phe levels.

2. METHOD

2.1 Design

A mixed between- and within- subjects design was used to compare adults with PKU with healthy controls.

2.2 Participants

20 adults with PKU and 20 healthy control participants took part in the study. A further 24 participants, who were significant others of the people in the PKU and Control groups also took part.

2.2.1 PKU group

The PKU participants were recruited from University College London Hospitals (UCLH).

In order to take part in the study, participants had to be aged between 18 and 65 years of age, to have been diagnosed with PKU and started on a low phenylalanine diet within the first month of life, and to have remained on-diet throughout their life. Remaining "on-diet" was defined as continuing to restrict intake of natural protein and taking supplements of amino acids, vitamins and minerals.

At the time of the study, there were 225 PKU patients between 18 and 65 years of age attending UCLH, making it the largest PKU population base in Europe. 161 (72%) of these patients had been diagnosed early (either through population screening or

because an older sibling was known to have PKU), and started on treatment within the first month of life. Before 1991, patients attending the clinic were advised to come off diet during childhood or adolescence. However, from 1991 onwards, patients have been advised to stay on diet for life. At the time of the study, 40 (25%) of the early-diagnosed patients had remained on a low phenylalanine diet throughout their life.

Exclusion criteria included having a diagnosis of neurological illness (other than PKU), psychiatric illness or alcohol or drug dependence. 2 patients were excluded from the study on these grounds. 2 patients were excluded from the study because their contact with the clinic had been intermittent, and so records of their metabolic control were sparse, and 1 was excluded because she was on a pre-conception diet (a particularly strict form of the low phenylalanine diet). A further 6 patients could not be contacted within the duration of the study (2 because they were overseas).

This left a total of 29 patients who were eligible to take part in the study, of whom 20 (69%) agreed to take part. The dietician at the Metabolic Clinic from which the participants were recruited was involved in the selection of participants for this study, and identified all the participants as people who had complied well with dietary treatment.

2.2.2 Control group

This group consisted of healthy adult volunteers who were matched to the PKU group for age, sex and Full-Scale IQ. Full-Scale IQ was estimated using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). For a description of the WASI see Section 2.4.1 below.

2.2.3 Significant others

Data were also collected from significant others for 14/20 (70%) of the participants in the PKU group and 10/20 (50%) of the participants in the Control group. Significant others were asked to fill in a short questionnaire (the DEX Questionnaire, see below). The missing data resulted from participants failing to return questionnaires.

2.2.4 Sample characteristics

Of the 20 PKU patients who participated, 18 had Type I PKU (pre-treatment Phe level > 1200 μmol/L) and 2 had Type II PKU (pre-treatment Phe level 600-1199 μmol/L).

As shown in Table 2a, there were no significant differences between the PKU and Control groups in terms of their age, years of education or Full-Scale IQ. (The mean scores for the PKU and Control groups on each of the sub-tests of the WASI are shown in Appendix A.) Both groups consisted of 12 males and 8 females.

For the PKU Group, 7 (50%) of the significant others who returned their questionnaires were a parent of the person with PKU, 4 (29%) were the partner of the person with PKU and 3 (21%) were another relative or friend. For the Control Group, 1 (10%) of the significant others was a parent, 5 (50%) were partners, and 4 (40%) were other relatives or friends.

2.3 Procedure

Ethical approval for this study was subsumed under the terms of existing ethical permission granted to Dr. Channon by the Joint University College London and University College London Hospitals' Committees on the Ethics of Human Research. This permission was originally granted in 1995 (see Appendix B), to cover a series of experimental studies involving patients with focal brain dysfunction. It was specified that patients with either structural or biochemical brain dysfunction would be studied, as well as matched healthy control participants, using standardised and experimental neuropsychological tests, self-report questionnaires and a clinical interview. The present study was covered by this permission because it compared patients with a biochemical disorder, PKU, and healthy control participants, and used measures of the type described in the original schedule. The original approval has been updated as necessary between 1995 and the present time, to take into account any amendments to the study protocol, and to include any new procedures required by the Ethics Committee. Amendments relevant to the present study have included updating the information and consent sheets and the advertisement for volunteers in 1998. Copies of these are appended, together with the standard letter written to participants (see Appendix C).

Each participant completed a series of neuropsychological tests within a single testing session. The session began with a short clinical interview, in order to ascertain the participant's educational and occupational background, and to establish that they did not have any medical or psychiatric history that would exclude them from the study.

Table 2a: Matching of groups for age, years of education and Full-Scale IQ

	PKU Group (N = 20)	Control Group (N = 20)	t	2-tailed sig.
	Mean (S.D.)	Mean (S.D.)		
Age	24.60 (4.62)	24.00 (3.96)	0.44	0.66
Years of Education	14.45 (1.79)	14.60 (1.43)	-0.29	0.77
Full-Scale IQ	111.75 (8.50)	112.00 (10.52)	-0.08	0.94

The neuropsychological tests were then administered in a fixed sequence, in order to ensure that the effects of practice or fatigue would be similar across participants. Participants were permitted to take breaks between tests as necessary in order to minimize the effects of fatigue.

2.4 Measures

2.4.1 Measure of general intellectual function

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

The WASI is designed to provide a short method of estimating intellectual function, and is linked to the Wechsler Adult Intelligence Scale - Third Edition (WAIS-III; Wechsler, 1997). It consists of four sub-tests: Vocabulary, Similarities, Matrix Reasoning and Block Design.

The Vocabulary sub-test is a 42-item task, in which the participant is asked to define a set of orally and visually presented words. It is considered to be a good measure of crystallized intelligence and general intelligence (Wechsler, 1999).

The Similarities sub-test is a 26-item task, in which the participant is asked to say how two orally presented words (e.g. "SMOOTH" and "ROUGH") are related. It is a measure of verbal concept formation, abstract verbal reasoning and general intelligence (Wechsler, 1999). Together, Vocabulary and Similarities provide the Verbal IQ (VIQ), which is a measure of crystallized abilities.

The Block Design sub-test is a 13-item task, in which the participant is required to copy a set of two-dimensional geometric patterns within a specified time-limit using two-colour cubes. It is considered to be a measure of perceptual organization and general intelligence (Wechsler, 1999).

Finally, the Matrix Reasoning sub-test is a 35-item task, in which the participant is presented with an incomplete pattern and must choose which of 5 additional pieces is the correct one to complete the pattern. It is a measure of nonverbal fluid reasoning and general intelligence (Wechsler, 1999). Together, Matrix Reasoning and Block Design provide the Performance IQ (PIQ).

Taken together, these four sub-tests provide the Full Scale IQ score (FSIQ), which is an estimate of general intellectual ability.

Wechsler (1999) reports evidence to support the reliability and validity of the WASI as a test of general intelligence. Internal consistency reliability coefficients of 0.96, 0.96 and 0.98 are reported for the VIQ, PIQ and FSIQ respectively, while test-retest reliability coefficients for these sub-tests are 0.87, 0.92 and 0.92 respectively. Validity studies have shown that WASI FSIQ scores account for 85% of the variance in WAIS-III FSIQ scores (Wechsler, 1999).

2.4.2 Measures of executive functions

2.4.2.1 Working memory

The Brixton Test (Burgess & Shallice, 1997)

In this test, the participant is shown a 56 page booklet, which has the same basic design on each page. This design consists of 10 circles, arranged in two rows of 5. One circle on each page is always coloured in, but the position of the coloured circle moves around following various patterns that come and go without warning. The participant is asked to indicate, on each page, where they think the coloured circle will appear on the next page.

The Brixton test yields a score (range 1 to 54), which is based on the total number of errors made. Burgess & Shallice suggest that this test is sensitive to problems in rule detection and tendencies toward impulsive behaviour. They estimated the split-half reliability of the test to be 0.62 ($p < 0.001$), based on the performance of a group of 121 healthy participants. They also report test-retest reliability of 0.71 ($p < 0.001$) for a group of 31 healthy participants.

Self-Ordered Pointing (Petrides & Milner, 1982)

On each trial of this test, the participant is presented with a series of pages, each of which shows the same set of words, presented in a grid layout. The location of the words changes on each page. The participant must touch one word on each page, touching a different word each time, so that by the end of the trial they have touched each word once. The test gradually increases in difficulty, with the number of words on

each page increasing from three, to six, to nine and finally to twelve. Three trials are conducted at each of these levels of difficulty.

This test yields two measures - one based on the number of correct responses at each level of difficulty, and one based on the time taken to complete each trial. Petrides (1991) has argued that this task demands on-line monitoring, and hence requires working memory.

2.4.2.2 Response initiation and suppression

The Hayling Test (Burgess & Shallice, 1997)

In this test, the examiner reads aloud a series of sentences, each of which has the last word missing. In Section 1 (15 items), the participant is asked to provide a word which completes the sentence, as quickly as they can (e.g. "The wealthy child attended a private ..." "SCHOOL"). In Section 2 (15 items), they are asked to provide a word which does not fit at the end of the sentence, and which is completely unrelated to the sentence in every way (e.g. "London is a very busy ..." "BANANA"), again responding as quickly as they can.

The Hayling Test provides three measures that are related to executive functions. The sum of the participant's response latencies in Section 1 provides a measure of simple response initiation speed. Section 2 provides two measures of response suppression ability (time taken to respond and an error score). Burgess & Shallice (1997) suggest that good performance on Section 2 of this task is likely to be associated with the use of strategies to deal with the response-suppression demands of the test (e.g. a participant might give with the names of objects that they can see in the room).

Burgess & Shallice (1997) report split-half reliabilities of between 0.35 to 0.83 ($p < 0.001$) for the measures obtained from the Hayling Tests, based on the performance of a group of 118 healthy participants. Split-half reliabilities for their group of patients with frontal-lobe lesions were higher ($N = 47$), ranging from 0.72 to 0.93 ($p < 0.001$). They also report test-retest reliabilities of between 0.52 and 0.78 ($p < 0.001$) for the measures obtained for this test for healthy controls ($N = 31$).

Letter Fluency

In letter fluency tasks, participants are typically asked to give as many words as they can think of that begin with a certain letter, within a given time limit. In this case, participants were asked to write down as many words as they could think of beginning with the letter "S" (excluding proper nouns, numbers and words sharing the same root) within a five minute time limit. Scoring was based on the number of acceptable words produced. As noted in the Introduction, it has been argued that Letter Fluency requires both response initiation and suppression, as participants must both retrieve appropriate words, and suppress inappropriate words (Perrett, 1974).

2.4.2.3 Attention

The Test of Everyday Attention (TEA; Robertson, Ward, Ridgeway & Nimmo-Smith, 1994)

The TEA consists of 8 sub-tests, which are designed to measure different types of attention using relatively familiar, everyday materials. It draws on Posner & Peterson's (1990) model of attention, which incorporates separate systems for selective attention, sustained attention and orientation. The TEA is designed to assess the first two of

these three systems. There are three parallel Versions of this test, of which Version A was used in this study. Two of the 8 sub-tests were administered.

(i) Telephone Search

In this sub-test, participants are asked to search through a "telephone directory" for particular symbols. Scoring is based on both the speed and accuracy of their search. In their analysis of normal subject data, Robertson et al. (1994) found that this sub-test loaded on a "selective attention" factor.

(ii) Telephone Search with Counting

Here, participants have to search through the telephone directory for particular symbols, as in the last sub-test, while simultaneously counting a series of tones presented on a tape recorder. Robertson et al. (1994) found that this sub-test loaded on a "sustained attention" factor in their analysis.

Scoring for both Telephone Search and Telephone Search with Counting is based on the number of symbols found, and the time taken to complete the search. Telephone Search with Counting also yields a score for the tone-counting element of the task, which consists of the proportion of tone sequences counted correctly.

Robertson et al. (1994) report good test-retest reliability for Telephone Search (Pearson coefficient = 0.86), based on the performance of a group of 118 healthy participants. They report lower reliability for Telephone Search while Counting (Pearson coefficient = 0.59), which they suggest may be the result of large learning effects across the tasks. All of the sub-tests in the TEA have been validated on healthy controls, people with stroke and people with closed head injury.

2.4.3 Measures of recall and recognition memory

Rey Auditory Verbal Learning Test (Rey, 1964; Taylor, 1959)

On Trials I to V of this test, the examiner reads aloud a list of 15 words (List A), at a rate of one per second. On each trial, the participant must repeat back as many words as they can remember. The examiner then reads a second list of 15 words (List B) for the participant to remember. On Trial VI, the participant is then tested for free recall of List A, without further presentation of this list. In this study, a delayed recall trial for List A was also given after 30 minutes (Trial VII). This was followed by a delayed recognition trial, in which the participant was asked to look through a list of 50 words (15 from List A, 15 from List B and 20 phonemically or semantically related foils) and indicate which words they recognized from *either* List A or List B.

The RAVLT is a test of verbal learning and memory (Lezak, 1995; Spreen & Strauss, 1991). In this study, it was used to derive measures of short-term recall (total correct for Trials I to V), delayed recall (total correct for Trial VII) and recognition (total correct minus false positives).

Spreen & Strauss (1991) describe the RAVLT as having modest test-retest reliability, with correlation coefficients of about 0.55 (see Snow et al., 1988).

Complex Figure Test (CFT; Rey, 1941; Osterrieth, 1944)

There are a number of different methods of administering and scoring this test (see, for example, Lezak, 1995). In this study, participants were first asked to copy Rey's complex line drawing. They were not told that they would later be asked to recall the

figure. A Delayed Recall trial was administered 40 minutes later, in which participants were asked to draw what they could remember of the original drawing.

This Delayed Recall trial was assessed using a 36-point scoring system (Lezak, 1995). According to this system, the figure is broken down into 18 elements, and points are awarded for the accuracy with which each element is reproduced and positioned. This provides a measure of visuo-spatial memory (Spreen & Strauss, 1991). Meyers & Meyers (1995) have reported a median inter-rater reliability coefficient (Pearson product-moment correlation) of 0.94 and a test-retest correlation coefficient of 0.89 for Delayed Recall (using a 30 minute delay).

Complex Figure Recognition (Meyers & Meyers, 1995)

This task is administered immediately after the Delayed Recall trial of the CFT. The participant is given a set of 24 line drawings, half of which formed part of the original complex figure, and half of which did not. The participant is asked to indicate whether or not they think that each drawing formed part of the original figure. The test yields a score out of 24, and provides a measure of recognition memory. Meyers & Meyers (1995) report a test-retest correlation coefficient of 0.87 for this test.

2.4.4 Measures of psychiatric symptomatology

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983)

The HADS was designed to detect clinical cases of anxiety and depression in medical outpatient settings, without undue influence of scores by physical symptoms. It is a 14-item self-report scale which consists of two sub-scales, assessing state anxiety (7 items) and depression (7 items). For each item, respondents must indicate which of

four possible replies comes closest to how they have been feeling over the preceding week. Scores on the individual items are summed to provide a score between 0 and 21 for each of the sub-scales, with higher scores indicating higher levels of anxiety or depression. Cut-off scores for probable clinical levels of disorder are provided.

Johnston, Wright & Weinman (1995) cite a number of studies which suggest that the HADS has good psychometric properties. For example, Moorey et al. (1991) report internal consistency of 0.93 for anxiety and 0.90 for depression, as measured by Cronbach's alpha. Zigmond & Snaith (1983) assessed the concurrent validity of the HADS by comparing scores with the results of psychiatric assessment for 100 medical outpatients, and found significant correlations for both anxiety and depression ($r = 0.54$ and 0.79 respectively). Moorey et al. also confirmed the construct validity of the HADS as a measure of two factors in their factor analysis of the responses of 568 cancer patients.

2.4.5 Measure of impact of PKU on everyday life

The Dysexecutive Questionnaire (DEX; Wilson, Alderman, Burgess, Emslie & Evans, 1996)

The DEX is a self-report questionnaire, which is included with the BADS (Behavioural Assessment of the Dysexecutive Syndrome) test battery (Wilson et al., 1996). It consists of 20 items, which are designed to address difficulties that are associated with the dysexecutive syndrome. The items are designed to cover potential changes in four areas, namely: emotion and personality, motivation, behaviour and cognition (following Stuss & Benson, 1984; 1986). Participants are asked to rate on a 5-point scale how

often they experience each of these problems (where 0 = "never" and 4 = "very often"). These scores are summed to provide a total score out of 80.

There are two versions of the DEX. One is designed to be completed by the person being assessed, and the other is designed to be completed by a person who has close contact with them (e.g. a relative). The two versions are almost identical, and have only small differences in phrasing. Both versions were used in this study.

2.4.6 Measures of metabolic control

PKU patients attending UCLH send in Guthrie tests each month, so that their blood Phe levels can be monitored. When they attend the clinic (on a sixth-monthly basis), their blood Phe level is tested using High Performance Liquid Chromatography (HPLC). The following measures of metabolic control were used in this study (following Stemerdink et al., 1999): (i) Concurrent Phe (the most recent blood Phe level obtained); (ii) Recent Phe (mean monthly blood Phe level for the two years preceding testing). Unfortunately, lifelong Phe levels could not be assessed in this study, as the relevant clinical data were not available.

3. RESULTS

3.1 Analysis of the data

The data obtained from each of the measures used were first examined to determine the extent to which they met the assumptions necessary for the use of parametric tests.

The normality of the distribution of data for each measure was established by converting the data to z-scores, and examining the distribution of these scores for outliers (using a criterion of +/- 3 standard deviations from the mean). Outliers were identified separately for the PKU and Control groups. Where there were outliers in the distribution of data for a particular measure, the data were transformed so that they more closely approximated a normal distribution. Log transformations were used in cases where the distribution was positively skewed (The Hayling Test (time taken) and Self-Ordered Pointing (time taken)), and the data were squared in cases where the distribution was negatively skewed (Block Design). In both cases the data were re-examined following the transformation in order to ensure that they approximated a normal distribution. For clarity, all descriptive statistics are reported using untransformed variables.

For measures where the data met the assumptions made by parametric tests, two types of data analysis were used. Some of the tests used yielded two or more measures that were sufficiently similar to compare directly in the same analysis (e.g. The Hayling Test, Part A and Part B). In these cases, the data were analyzed using Mixed ANOVAs, with Task (e.g. Part A versus Part B) as the within-group variable and Group (PKU versus Control) as the between-groups variable. A multivariate approach to repeated

measures was used in these analyses. For the remainder of the measures where the data were suitable for the use of parametric tests, independent samples t-tests were used to compare the performance of the PKU and Control groups. In one case where Levene's test indicated that the variances of the two groups were significantly different (The Brixton Test), the results of a t-test that did not assume equal variances are reported.

For all measures where the data were not suitable for the use of parametric tests, Mann-Whitney tests were used to compare the performance of the PKU and Control groups.

Other than for the DEX Other questionnaire (which 40% of participants did not return), there were very few missing data points in the data set (4 in all). Where data were missing, the relevant participants were excluded from the relevant analyses.

3.2 Results for measures of executive functions

3.2.1 Working memory

The descriptive data for the tests of working memory are shown in Table 3a.

The scores for the PKU and Control groups on The Brixton Test were compared using an independent samples t-test. This showed that there was no significant difference between the scores of the two groups on this test ($t = 1.15$, $df = 31$; 2-tailed $p = 0.26$).

For Self-Ordered Pointing (time taken), a 3 x 2 Mixed ANOVA showed that there was a significant effect of the size of the array (i.e. 6, 9 or 12 words) ($F(2, 36) = 448.22$, $p < 0.001$). There was also a significant effect of Group ($F(1, 37) = 18.73$, $p < 0.001$). However, there was no significant interaction between the Size of Array and Group ($F(2, 36) = 0.29$, $p = 0.75$). The data in Table 3a show that, unsurprisingly, participants took longer to complete the task as the number of words in the array increased. The PKU group was also slower than the Control group to complete the task. However, the response times of the PKU group were not disproportionately affected by increases in the size of the arrays.

For Self-Ordered Pointing (number correct), a 3 x 2 Mixed ANOVA showed that there was again a significant effect of the size of the array ($F(2, 37) = 848.81$, $p < 0.001$). However, there was no significant effect of Group ($F(1, 38) = 0.53$, $p = 0.47$), and no significant interaction between the size of the array and Group ($F(2,37) = 2.78$, $p = 0.08$). Table 3a shows that the participants made more errors as the number of words in the array increased. However, there was no difference between the groups in terms of the number of errors made, or in terms of the effect of larger arrays on their accuracy in completing the task.

Table 3a: Performance on tests of working memory

Task	PKU Group	Control Group
	Mean (S.D.)	Mean (S.D.)
Brixton Test		
Errors (max=54)	13.25 (5.16)	11.70 (3.08)
Self-Ordered Pointing		
6 words (time taken in secs)	67.68 (13.78)	50.00 (11.81)
9 words (time taken in secs)	117.90 (24.83)	90.75 (20.95)
12 words (time taken in secs)	163.15 (38.20)	129.75 (36.61)
6 words – N correct (max=18)	16.50 (1.40)	17.05 (1.00)
9 words – N correct (max = 27)	24.40 (1.90)	23.90 (1.41)
12 words – N correct (max=36)	31.80 (2.71)	30.85 (1.76)

3.2.2 Response initiation and suppression

The descriptive data for the tests of response initiation and suppression are shown in Table 3b.

The scores of the two groups on Letter Fluency were compared using an independent samples t-test. This showed that there was a significant difference between the scores of the two groups on this test ($t = 12.60$, $df = 38$; 2-tailed $p = 0.01$). From Table 3b it can be seen that the PKU group produced fewer words than the Control group on this task.

For the Hayling Test (time taken), a 2 x 2 Mixed ANOVA showed that there was a significant effect of Task ($F(1, 38) = 17.37$, $p < 0.001$). It can be seen from Table 3b that both groups of participants were slower on Part B than Part A of the test. There was also a significant effect of Group ($F(1, 38) = 4.23$, $p < 0.05$), with the PKU group being slower than the Control group on both parts of the test. However, there was no significant interaction between Task and Group ($F(1,38) = 0.64$, $p = 0.43$). Hence, the response time data suggest that, while both groups of participants found Part B of the test more difficult than Part A, the groups were not differentially affected by the different demands of Part A and Part B of the test. The error scores for Part B of the test were analyzed separately from the response time data, using a Mann-Whitney test. This showed that there was no significant difference between the error scores for the two groups ($U = 147.50$; $p = 0.14$). Hence it does not seem to be the case that either group maintained their speed on Part B of the test by sacrificing accuracy on the task more than the other group did.

Table 3b: Performance on tests of response initiation and suppression

Task	PKU Group	Control Group
	Mean (S.D.)	Mean (S.D.)
Fluency		
Total Words Produced	40.05 (8.20)	48.80 (12.64)
Hayling Test		
Part A (time taken in secs)	10.60 (5.19)	6.00 (4.65)
Part B (time taken in secs)	24.35 (23.14)	22.00 (22.81)
Part B Error Score	1.90 (1.68)	1.35 (1.98)

3.2.3 Attention

The descriptive data for the tests of attention are shown in Table 3c.

Mixed ANOVAs were used to compare participants' performance on Telephone Search with their performance on Telephone Search with Counting. For Telephone Search (time taken), a 2 x 2 ANOVA showed that there was no significant effect of Task (Telephone Search versus Telephone Search with Counting) ($F(1, 38) = 0.08$, $p = 0.78$). There was, however, a significant effect of Group ($F(1, 38) = 11.58$, $p < 0.005$), with the Control group completing both tasks more quickly than the PKU group. However, there was no significant interaction between Task and Group ($F(1, 38) = 2.35$, $p = 0.13$). Hence the PKU group performed both the "selective attention" and "sustained attention" tasks more slowly than the Control group, but their response times were not differentially affected by the different nature of the two tasks.

A mixed ANOVA was also used to compare participants' performance on Telephone Search and Telephone Search with Counting (Number of symbols counted). It should be noted that this approach to the analysis of this data is not ideal, as the data were not normally distributed because of a ceiling effect. However, this approach was adopted because there is no equivalent non-parametric test with which to compare the data across the two tests. The 2 x 2 ANOVA that was used showed that there was a significant effect of Task ($F(1, 38) = 15.83$, $p < 0.001$). It can be seen from Table 3c that participants counted fewer symbols during Telephone Search with Counting than during Telephone Search.

There was, however, no significant effect of Group ($F(1, 38) = 2.80$, $p = 0.10$), and no significant interaction between Task and Group ($F(1, 38) = 2.42$, $p = 0.13$). Hence, while both groups counted fewer symbols in Telephone Search with Counting than in Telephone Search, there were no significant differences between the patterns of scores obtained by the two groups.

The data from the tone-counting element of Telephone Search with Counting were analyzed separately, using a Mann-Whitney test. This showed that there was no significant difference between the groups in terms of the proportion of tones that they counted correctly ($U = 189.00$, $p = 0.96$). Hence it does not seem to be the case that either group maintained their performance on the Telephone Search task at the expense of their performance on the Counting task more than the other group did.

Overall, the results of the tests reported so far suggest that the PKU group performed more poorly than the Control group on several of the tests of executive function. Tests on which significant differences were found between the two groups included one of the tests of Working Memory (SOP), both of the tests of Response Initiation and Suppression and both of the tests of Attention. However, the differences between the groups were subtle and, for the most part, reflected in differences in response times rather than differences in accuracy.

Table 3c: Performance on tests of attention

Task	PKU Group	Control Group
	Mean (S.D.)	Mean (S.D.)
TEA		
Telephone Search		
- time taken in secs	61.35 (16.06)	49.75 (9.68)
- N symbols counted (max = 20)	19.25 (1.02)	18.95 (1.05)
Telephone Search with Counting		
- time taken in secs	64.20 (16.70)	47.80 (12.04)
- N symbols counted (max = 20)	18.55 (1.43)	17.35 (2.68)
- proportion of tones correct	0.95 (0.12)	0.95 (0.13)

3.3 Results for measures of recall and recognition memory

The results for the tests of recall and recognition memory are shown in Table 3d.

The scores of the PKU and Control groups on the tests of recall and recognition memory were analyzed using independent samples t-tests and Mann-Whitney tests, as appropriate. It can be seen from Table 3d that there were no significant differences between the PKU and Control groups on any of these measures.

The fact that no significant differences were observed between the scores of the PKU and Control groups on any of the memory tests used contrasts with the significant differences that were found between the groups on several of the tests of executive function. However, as noted above, the significant differences between the groups on the executive measures were largely reflected in differences in response times rather than differences in accuracy. Unfortunately, the memory tests that were used in this study did not include any timed measures with which participants' performance on the timed executive measures could be compared directly. This raises the possibility that the PKU group were simply slower than the Control group on all timed tests, regardless of their nature. However, response speed is very important for Block Design, which is one of the subtests of the WASI, on which participants were originally matched. The scores for the two groups on Block Design were therefore compared, in order to assess the possibility that the PKU group were simply slower than the Control group on all timed tests. An independent samples t-test showed that there was no significant difference between the scores of the two groups on this test ($t = -1.27$, $df = 1$, $p = 0.21$). This result undermines the hypothesis that the PKU group was simply impaired on all tasks that required speed, regardless of their nature.

Table 3d: Performance on measures of recall and recognition memory

	PKU Group	Control Group	Test Statistic	2-tailed sig.
	Mean (S.D.)	Mean (S.D.)		
Complex Figure Test				
Recall (max=36)	22.80 (6.86)	25.43 (6.69)	t = -1.23	0.23
Recognition (max=24)	21.15 (1.57)	21.55 (1.82)	t = -0.75	0.46
RAVLT				
Trials I-V (max=75)	55.55 (7.64)	57.90 (8.77)	t = -0.90	0.37
Delayed Recall (max=15)	11.35 (2.92)	12.10 (2.88)	t = -0.82	0.42
Recognition (max=30)	20.70 (4.39)	19.95 (4.02)	t = 0.56	0.58

3.4 Results for measures of psychiatric symptomatology

Table 3e shows the results for the two groups on the HADS, which was used as a measure of psychiatric symptomatology in this study.

The results for this measure were analyzed using a 2 x 2 Mixed ANOVA, where the within-group variable was Symptom Type (Anxiety versus Depression), and the between groups variable was Group (PKU versus Control). This analysis showed that there was a significant main effect of Symptom Type ($F(1, 37) = 74.32$, $p < 0.001$). As can be seen from Table 3e, participants reported more anxiety-related symptoms than depression-related symptoms. However, there was no main effect of Group ($F(1, 37) = 0.08$, $p = 0.77$), and no significant interaction between Task and Group ($F(1, 37) = 0.03$, $p = 0.87$). Hence it seems that there was no significant difference between the groups in terms of the number of symptoms reported, and that both groups of participants tended to report more anxiety-related symptoms than depression-related symptoms.

3.5 Results for measure of impact of PKU on everyday life

Table 3f shows the results obtained from the DEX questionnaire, which was used as a measure of dysexecutive behaviours in everyday life.

Table 3e: Results for measures of psychiatric symptomatology

Task	PKU Group	Control Group
	Mean (S.D.)	Mean (S.D.)
HADS		
Anxiety Scale (max=21)	6.20 (3.37)	6.47 (2.06)
Depression Scale (max=21)	2.25 (2.36)	2.37 (2.24)

Table 3f: Results for measure of impact of PKU on everyday life

	PKU Group	Control Group	T	2-tailed sig.
	Mean (S.D.)	Mean (S.D.)		
DEX				
Self (max=80)	16.95 (7.86)	21.47 (7.87)	-1.80	0.46
Other (max=80)	10.93 (6.41)	16.10 (10.95)	-1.46	0.16

Results from both the version of the questionnaire that participants completed themselves (DEX Self) and the version completed by someone who knew them well (DEX Other) were analyzed using independent samples t-tests. It should be noted that only 14/20 (70%) of the PKU Group and 10/20 (50%) of the Control Group returned the DEX Other questionnaire. From Table 3f it can be seen that there was not any significant difference between the groups in terms of the extent to which they rated themselves as showing behaviours associated with the dysexecutive syndrome. There was also no significant difference between the groups in terms of the extent to which people who knew them well rated them as showing behaviours of this type.

3.6 Results for measures of metabolic control

Two measures of metabolic control were used for the PKU participants in this study: (i) Concurrent Phe (the most recent Phe level obtained) and (ii) Recent Phe (the mean monthly Phe level for the two years preceding cognitive testing). The participants were found to have a mean Concurrent Phe level of 858.80 μmol/l (S.D. = 477.72), and a mean Recent Phe value of 780.40 μmol/l (S.D. = 418.35).

Correlations were calculated between the Concurrent Phe and Recent Phe measures, and each of the cognitive measures described above. Pearson's correlations were used where parametric tests were appropriate, and Spearman's correlations were used where non-parametric tests were more appropriate. Only two of these correlations reached significance at the $p < 0.05$ level. For SOP, there were significant positive correlations between Concurrent Phe and Time Taken ($r = 0.50$, $p = 0.03$) when there were 9 words, and Number Correct ($r = 0.50$, $p = 0.03$) when there were 12 words. However, given the large number of correlations that were calculated (N = 27), this

number of putatively significant correlations could well have arisen by chance. It is also important to note that correlation coefficients computed with a small sample size such as this (N = 20) are known to be unstable, and should be interpreted with caution.

4. DISCUSSION

4.1 Summary of main findings

This study compared the cognitive profile of a group of adults with early and continuously treated PKU with that of a group of controls matched for age, sex and IQ.

Despite the fact that the two groups had similar IQ levels, the PKU group was found to be impaired relative to the Control group on several different tests of executive function. Tests on which impairments were observed included tests believed to involve working memory (SOP), response initiation and suppression (Letter Fluency and The Hayling Test) and attention (Telephone Search and Telephone Search with Counting). Only one test of executive function (The Brixton Test) failed to show any significant difference between the groups. However, the differences between the groups were subtle and, for the most part, reflected in differences in response times rather than differences in accuracy. By contrast, there were no significant differences between the groups on either of the tests of memory function that were used. This was in spite of the fact that these tests yielded measures of both free recall (which is thought to involve some contribution from executive functions) and recognition (which is thought to make fewer demands on executive functions).

Although there were significant differences between the groups on the tests of executive function, few significant correlations were found between the PKU participants' blood Phe levels and their scores on the neuropsychological tests. There was also no significant difference between the groups in terms of the number of dysexecutive symptoms that they showed in everyday life, as assessed by the DEX

questionnaire. Finally, there was no significant difference between the PKU and Control groups in terms of the number of psychiatric symptoms that they reported on the HADS.

4.2 Characteristics of the PKU group

Before considering the results obtained on the neuropsychological measures used in this study, it is worth considering the broad characteristics of the PKU group who took part, in order to provide a context within which to consider the neuropsychological test results. Two issues seem to merit particular consideration: participants' IQ scores and their blood Phe levels.

4.2.1 IQ

As noted in the Introduction, the PKU and Control groups in this study were matched on IQ. This means that the results of the study cannot be used to assess whether the PKU participants achieved the level of cognitive abilities that they would have achieved if they had not had this condition. However, one noteworthy aspect of the results obtained in this study is that the participants in the PKU group achieved an average IQ score of 112 (S.D. = 8.5). This score is in the high average range, and is higher than the mean IQ scores that have been reported in previous studies of treated PKU. For example, studies of children with early and continuously treated PKU have typically reported finding mean IQ scores in the 80s or 90s (Berry et al., 1979; Dobson et al., 1976; Waisbren et al., 1987; Williamson et al., 1981). Similarly, Pietz et al. (1998) found that their group of early and continuously-treated adults achieved a mean IQ score of 98.

There are several possible explanations for the difference between the results of the present study and previous findings. One possibility is that the discrepancy reflects differences between the measures used in the different studies. However, in their study of adults with treated PKU, Pietz. et al. assessed IQ using the German version of the WAIS-R, and it seems unlikely that a discrepancy of this size could reflect differences between measures taken from the same family of tests.

Another possible argument would be that the discrepancy between the present results and those obtained in studies of continuously treated children could have arisen because people with higher IQs remain on diet for longer. Or, conversely, it could be argued that continued treatment into adulthood has beneficial effects on IQ scores. However, neither of these explanations can account for the discrepancy between the present results and those obtained by Pietz et al., as the latter were also obtained with a group of continuously treated adults. Furthermore, Pietz et al. found that, for their participants, there was no evidence of any change in IQ scores after the age of 12.

Another potential explanation is that the discrepancy in mean IQ scores reflects better metabolic control achieved by the participants in the present study. However, while it is possible that the current group of participants did have better metabolic control than the participants in the Pietz et al. study (see Section 4.2.2 below), it is unlikely that they achieved better control than participants in studies of children with treated PKU, as Phe levels are typically monitored very closely in young children.

A more plausible explanation is that the higher score observed in the present group reflected some sort of selection bias in terms of those patients who agreed to take part. While 69% of eligible patients agreed to take part in this study, 92% of eligible

participants took part in the study carried out by Pietz et al. Hence the higher mean IQ score obtained in the present study may have occurred because people with higher IQs were more willing to take part. It does seem plausible that this would be the case, as taking part in cognitive testing is likely to be more rewarding for people who perform better on such tests. If this is indeed the correct explanation for the high IQ scores, then this suggests that the results obtained in this study reflect the upper range of ability in people with treated PKU.

Another important issue to note is that the PKU participants were able to achieve a mean IQ score that was in the high average range, despite the fact that there was evidence from the tests of executive function that they actually showed subtle cognitive deficits. The insensitivity of IQ tests to frontal damage has long been recognized. For example, early reports that patients with frontal damage were unimpaired on IQ tests (e.g. Hebb, 1939) led to the belief that the frontal lobes were "silent". Although later studies have demonstrated that decreases in IQ can occur following frontal damage (Milner, 1964; Smith, 1966; Tow, 1955), it has been recognized that decreases in IQ may be small in relation to the very severe difficulties in everyday life that may result from frontal damage (Blumer & Benson, 1975; Damasio, 1985). The current finding that the PKU group was able to achieve a mean IQ score in the high average range, despite showing subtle deficits on tests of executive function, therefore emphasizes how important it is that sensitive measures are used in studies of outcome in treated PKU.

4.2.2 Concurrent Phe Levels

As noted in the Method section, all of the participants involved in this study were known by the dietician at their Metabolic Clinic to comply well with dietary treatment. However, despite having remained "on diet" throughout their lives (as defined by continuing to restrict natural protein and taking appropriate dietary supplements), they were found to have a mean Concurrent Phe level at the time of testing of 858.80 μmol/l (S.D. = 477.72), and a mean Recent Phe value (i.e. mean monthly Phe level for the two years preceding testing) of 780.40 μmol/l (S.D. = 418.35). These figures suggest that, while the PKU group was, at least to some extent, continuing to adhere to dietary treatment, their blood Phe levels were not below the upper limit of 700 μmol/l recommended by the Medical Research Council (1993b) for patients above school-age. This means that the results obtained with this group of participants cannot be used to assess cognitive outcome in patients whose blood Phe levels have remained within recommended limits, as was originally planned. However, the mean Phe level of the participants in this study was lower than the mean Phe level of participants in any of the other studies of adults with treated PKU that have been reported to date. For example, in their study of early-treated adults (who were off-diet, or on poorly controlled diets), Smith, Klim, Mallozzi & Hanley (1996) found that the mean concurrent Phe level of participants was 1056 μmol/l. Similarly, in their study of early-treated adults (of whom only 10/25 had achieved continuous dietary adherence), Ris et al. (1994) found that participants had a mean concurrent Phe level of 1320 μmol/l. Finally, Pietz et al. (1998) found that their group of continuously treated participants had a mean concurrent Phe level of 1085 μmol/l. Hence, while the results obtained with the current group cannot inform us about cognitive outcome in patients whose blood Phe levels have remained within strict

recommended limits, they can help to inform us about outcome in adults with lower blood Phe levels than have been previously reported.

It is also important to note that, while the Medical Research Council (1993b) guidelines recommend that blood Phe levels should be kept below 700 μmol/l in patients above school age, it is widely recognized that, in practice, this is very difficult to achieve. Hence, while the Medical Research guidelines suggest that, in older children, "every effort should be made to continue treatment at blood phenylalanine concentrations no higher than 700 μmol/l", they also acknowledge that "given the major practical difficulties of treatment, especially in subjects with severe forms of phenylalanine hydroxylase deficiency, adolescents and young adults will have to make their own choices about their phenylalanine intake, having been appraised of the risks of high phenylalanine concentrations" (1993b, p. 427). Clinical experience at the UCLH clinic from which the PKU participants were recruited also suggests that, in fact, few patients are able to achieve blood Phe levels that are consistently below 700 μmol/l.

4.3 Performance on neuropsychological tests

As noted above, the PKU group in this study was found to be impaired relative to the Control group on one of the tests of working memory (SOP), both of the tests of response initiation and suppression and both of the tests of attention. By contrast, the PKU group did not seem to show any impairment relative to controls on either of the memory tests that were used. Hence the results obtained in this study appear to suggest that the PKU showed an apparently selective deficit on tests making greater demands on executive functions. However, before considering the implications of a

selective deficit of this nature, it is important to consider other possible interpretations of the pattern of results obtained.

One feature of these results in particular makes their interpretation less than straightforward. This is the fact that, in all cases where significant differences were found between the groups, these occurred on tests that were timed in some way. In most cases, differences between the groups were reflected in slower response times by the PKU group. (The lower score of the PKU group on Letter Fluency was slightly different, in that in this case the PKU group produced fewer responses than the Controls within an allotted time.) Unfortunately, the memory tests did not include any timed tests with which the timed executive tests could be compared directly. This raises the possibility that the apparent difference between the performance of the PKU and Control groups on the tests of executive function and the memory tests was some kind of artifact, resulting from the fact that the former involved a timed element, while the latter did not.

4.4 The relationship between speed and accuracy

The problem of how to measure people's ability on tasks where both speed and accuracy can be measured is well-recognised (see for example, Dennis & Evans, 1996). The difficulty arises because the time taken to complete a test depends on the accuracy with which it is completed. Individuals may also differ in terms of the compromise that they choose to strike between speed and accuracy on any particular test. This "speed-accuracy trade-off" means that it is difficult to consider either accuracy scores or response latencies in isolation.

Because of the potential for speed-accuracy trade-offs in this study, there are several possible interpretations of the pattern of results obtained. First, it could be argued that the PKU group was selectively impaired on tests of executive function, as predicted by the executive deficit hypothesis, and that this impairment was indicated by the PKU group's longer response times on executive tests. According to this hypothesis, it could be argued that the PKU group only achieved accuracy levels equivalent to the Control group on these tests by sacrificing speed. A second potential hypothesis is that the PKU group was actually less able than the Control group on both the executive and memory tests, but maintained accuracy on these tests by sacrificing speed. It could be argued that this global deficit would not be apparent on the memory tests, as these tests were not timed. Finally, it could be argued that the PKU group was actually of equal ability to the Control group, but that they simply chose to take more time over the timed tests. This would give the impression of a selective deficit on tests of executive function, as these tests were timed and the memory tests were not. However, there are a number of reasons to suggest that the latter two hypotheses cannot account for the overall pattern of results obtained in this study.

First, although neither of the memory tests used in this study were timed, response speed is crucial in calculating scores for Block Design (which is one of the sub-tests of the WASI). As reported in the Results section, a post-hoc comparison showed that there was no significant difference between the performance of the PKU and Control groups on this measure. This suggests that the PKU group did not show slower response times than the Controls on all timed tests, and hence supports the view that their slower response times on the tests of executive function were due to the greater executive demands imposed by those tests.

Further evidence as to whether the results of this study are consistent with the PKU group showing a selective deficit for executive functions can be obtained from a more detailed consideration of the extent to which there may have been "speed-accuracy trade-offs" in participants' performance on each of the tests used in this study.

First, for two of the tests of executive function (The Hayling Test and Telephone Search), both groups of participants achieved very high levels of accuracy, while the PKU group responded more slowly than the Control group. At first, the equivalent levels of accuracy achieved by the two groups might suggest that it would be reasonable to make a direct comparison between the response latencies of the two groups. However, ceiling effects in the accuracy data for both of these tests means that these data are difficult to interpret. Hence, while it may have been the case that the PKU participants were only able to maintain accuracy on these tests by sacrificing speed, it is not possible (because of the ceiling effects in the accuracy data) to rule out the alternative possibility that the PKU participants had the potential to respond more quickly without any appreciable fall in their accuracy.

The results from the Letter Fluency task may, however, be more informative as to the relative abilities of the two groups. For this task, participants had to produce as many words beginning with the letter "S" as they could in 5 minutes. What is particularly relevant to the present discussion is that this is actually quite a generous time limit for this task. Observation of participants while they were completing the task suggested that, after an initial rush of responses, their rate of responding tended to tail off very quickly. Hence, after an initial rush of responses that seemed to consist of words that immediately sprang to mind, it appeared that participants' ability to continue to produce further responses depended on their ability to generate strategies for doing so. This

observation suggests that scores on this task are less dependent on pure speed of responding than scores on the Hayling Test and Telephone Search. Hence, for this task, the significant difference between the scores obtained by the two groups provides more convincing evidence that the PKU participants were indeed of lower ability than the controls.

The two remaining tests of executive function (The Brixton Test and SOP) differed from those described above, in that lower accuracy rates were obtained by both groups of participants on these tests. As previously noted, there were no significant differences between the groups in terms of their accuracy on these tests. However, the PKU group performed SOP more slowly than the controls. This difference in response speed is perhaps more informative than the speed differences on The Hayling Test and Telephone Search, as in this case there was not a ceiling effect in the accuracy data. Hence, the slower response times of the PKU participants, in the context of equivalent accuracy rates for the two groups, suggest that the PKU group was indeed of lower ability than the Control group on SOP.

Finally, for both of the memory tests that were used in this study, accuracy was not at ceiling, and the PKU group achieved accuracy levels equivalent to the controls. One of the tests that was used (CFT) can be carried out at a participant's own pace, and hence it could be argued that the PKU group may have achieved accuracy levels equivalent to the controls by carrying out the test at a slower rate. However, in the other memory test that was used (RAVLT), stimuli are presented at a fixed pace by the examiner. This means that there is no opportunity for participants to carry out the task more slowly in order to maintain accuracy. In spite of this, there was no significant difference between the accuracy rates of the two groups on this task. This suggests that, on at least one of

the memory tasks that were used, the PKU group was able to achieve accuracy equivalent to the Control group, despite the fact that stimuli were presented at a fixed pace.

Overall, therefore, the pattern of results obtained in this study appears to provide some support for the view that the PKU group showed a selective deficit on tests of executive function. The PKU group appeared to show impairments across tests of working memory, response initiation and suppression and selective and sustained attention. Given ceiling effects in the accuracy data and the possibility that participants made speed-accuracy trade-offs in their performance, the apparent impairments observed on the tests of selective and sustained attention should perhaps be interpreted rather cautiously. However, significant differences between the groups on tests of working memory and response initiation and suppression were less easily explained in terms of speed-accuracy trade-offs. Hence participants were found to show impairments across tasks that are thought to make high demands on both the dorsolateral and ventrolateral prefrontal cortex, and potentially also on tasks that are though to make high demands on the anterior cingulate. In contrast to the results obtained on the tests of executive function, the PKU group did not show any deficits relative to controls on either of the memory tests that were used. These findings are therefore broadly consistent with Hypothesis [1], as described in the Introduction.

4.5 Implications for Psychological Models of PKU

As there were no clear differences between the patterns of results obtained on the tests of working memory, response initiation and suppression and attention, the results obtained on these tests will henceforth be discussed together, as the results obtained

on the tests of executive function. The fact that the PKU group appeared to show a selective deficit on these tests of executive function means that the results of this study are broadly consistent with the executive deficit hypothesis of treated PKU. Hence, the PKU group appeared to show a selective deficit for functions that are thought to make greater demands on the lateral prefrontal cortex, in the context of preserved performance on tasks that are thought to make fewer demands on this region. Furthermore, this pattern of results was obtained in a group that was matched to control participants on IQ. Matching groups on IQ in this way meant that this study provided a stringent test of the executive deficit hypothesis. This was because any deficits shown by the PKU group on the tests of executive function could not be attributed to lower general intelligence in this group. In addition, as executive functions are likely to make some contribution to performance on the tasks that make up intelligence tests, matching the groups on IQ means that, if anything, these results are likely to represent a conservative estimate of the executive deficits shown by the PKU group.

The pattern of results obtained in this study replicates the patterns of results that have been obtained in several studies of children with treated PKU (Diamond et al., 1997; Weglage et al., 1996; Welsh et al., 1990). These results are also consistent with the view that the selective impairment on tests of executive function that has been observed in children constitutes a long-term deficit, rather than a developmental lag, which will eventually disappear with continued treatment (see Mazzocco et al., 1994; Welsh & Pennington, 2000). However, it is important to note that participants' blood Phe levels were not within the limits currently recommended by the Medical Research Council. This means that it remains an open question as to whether the cognitive deficits that have been observed in this and other studies of people with treated PKU would be eliminated with stricter metabolic control. This is a question of some

theoretical importance, as the answer might help to clarify the mechanisms that underlie the cognitive deficits observed in treated PKU. In practical terms, however, it is questionable how many people are able to maintain blood Phe levels that are consistently below 700 μmol/l into adulthood.

Another important issue is that, while the results of this study suggest that continued treatment (to the extent that this was achieved in the current group) may not be sufficient to entirely eliminate cognitive deficits in people with treated PKU, they do suggest that there may be some benefits of staying on diet into adulthood. Hence, when the results obtained in this study are compared to those of other studies of adults with treated PKU, there is some evidence to suggest that the present group may have shown less marked cognitive deficits than people who have discontinued dietary treatment. For example, in their study of early-treated adults (who were off-diet or on poorly controlled diets), Smith, Klim, Mallozzi & Hanley (1996) found that the PKU group was impaired relative to controls on both tasks thought to be supported by prefrontal cortex and tasks thought to be supported by more posterior brain regions. Furthermore, in contrast to the findings in the present study, the PKU group showed impaired accuracy on SOP relative to IQ-matched controls. Similarly, Ris et al. (1994) found that their group of early-treated patients (of whom less than half had achieved continuous dietary adherence) showed impairments across a number of cognitive domains relative to sibling controls. In addition, one of the tests on which they found their PKU group to be impaired (CFT) did not produce any evidence of impairments in the PKU group in the current study. These findings provide indirect evidence to suggest that the PKU participants in the current study may have had less marked cognitive deficits than patients who have come off diet or who are on more poorly controlled diets. This is of some theoretical importance, in that it suggests that the

processes through which the cognitive deficits observed in treated PKU are mediated continue to exert an effect into adulthood.

Overall, the fact that there was some evidence to suggest that the PKU group showed a selective deficit on tests of executive function, means that the results of this study provide some support for the view that functions which make greater demands on lateral prefrontal cortex are selectively impaired in treated PKU. These findings are therefore broadly consistent with the executive deficit hypothesis of treated PKU.

4.6 Relationship between metabolic control and cognitive function

As noted in the Introduction, the results of previous studies have suggested that both concurrent Phe levels and lifetime Phe levels may influence the cognitive abilities of people with treated PKU. In this study, the relationships between Concurrent Phe levels and Recent Phe levels (covering the two years preceding testing) and cognitive performance were examined. Unfortunately, the influence of lifetime Phe levels could not be examined, as the relevant data were not available.

The fact that significant differences were observed between the cognitive abilities of the PKU and Control groups supports the general view that elevated Phe levels are associated with poorer cognitive functioning. However, as previously noted, very few significant correlations were found between the PKU participants' blood Phe levels and their performance on the neuropsychological tests. This finding could be taken to be inconsistent with the executive deficit hypothesis of treated PKU, according to which high concurrent Phe levels impair cognitive functioning. However, there are a number of possible alternative explanations for this finding.

First, as noted in the Introduction, previous findings on the relationship between concurrent Phe levels and cognitive performance have been equivocal. For example, several studies of continuously treated children have found negative correlations between performance on tests of executive function and concurrent Phe levels (Diamond et al., 1997; Weglage et al., 1996; Welsh et al., 1990), while other studies have failed to observe any significant relationship between these variables (Griffiths, Campbell & Robinson, 1998; Griffiths, Tarrini & Robinson, 1997). Griffiths and her colleagues (Griffiths, Campbell & Robinson, 1998) have suggested that the studies in which significant relationships have been observed between concurrent Phe levels and cognitive performance may be those in which participants have had higher concurrent blood Phe levels. Indeed, as previously noted, this hypothesis does seem to be able to account for several of the findings reported in the literature on children with treated PKU. However, it is difficult to make direct comparisons between the quality of metabolic control of participants in studies of children with treated PKU and participants in the present study, as different blood Phe levels are recommended for different age groups.

Within the adult literature, several studies have found evidence of a correlation between concurrent Phe levels and performance on tests of executive function. For example, Ris et al. (1994) found that, for their group of participants (of whom 10/25 remained on diet), concurrent Phe levels correlated with performance on the WCST and an attention task, but not with performance on the CFT. Similarly, Pietz et al. (1998) found that, for their group of early-treated adults, concurrent Phe levels influenced performance on an attention task. Finally, Smith et al. (1996), found that, for their group of participants (who were off diet, or on poorly controlled diets), both concurrent and lifetime Phe levels correlated with performance on tests of executive function. As noted above, the

participants in the present study had lower blood Phe levels than the participants in these other studies, and so it is possible that this may account for the fact that so few significant correlations were observed between Concurrent Phe levels and cognitive performance in this study.

Second, it is likely that the cognitive impairments shown by the PKU group in this study were mediated, at least partially, by lifetime blood Phe levels. This is suggested by the fact that several previous studies of adults with treated PKU have found evidence of a relationship between longer-term Phe control and cognitive function. For example, Pietz et al. (1998) found that both concurrent Phe levels and Phe levels from the age of 12 to adulthood influenced performance on an attention task. Similarly, Smith et al. (1996) found that performance on the WCST (but not the SOP or tests of posterior brain function) was related to lifetime Phe levels. Finally, Ris et al. (1994) found that performance on the WCST and the CFT (but not performance on an attention task) was related to the age at which participants came off diet. Furthermore, studies which have manipulated blood Phe levels experimentally have shown that, while reducing concurrent Phe levels can reduce cognitive deficits associated with high Phe levels, it does not return cognitive performance to the level of that of healthy controls (e.g. Schmidt et al., 1994; Schmidt et al., 1996). Findings such as these suggest that the cognitive performance of people with treated PKU is likely to be mediated by both long-term and concurrent Phe levels.

Finally, it is possible that the low number of correlations between Concurrent blood Phe levels and performance on the neuropsychological tasks reflects the fact that blood Phe levels may not predict brain Phe levels (see Koch et al., 2000). Future studies using MRS may help to clarify the relationship between brain Phe levels and cognitive

performance, and hence may provide a more adequate test of whether the cognitive deficits observed in treated PKU are mediated by the mechanisms which are proposed to do so by the executive deficit hypothesis.

Overall, the fact that participants' performance on executive tasks was not found to be associated with Concurrent or Recent blood Phe levels means that Hypothesis [2], as described in the Introduction, was not supported. However, as described above, there are a number of possible explanations for the lack of an observed association between these variables which would mean that these results are not necessarily incompatible with the executive deficit hypothesis of treated PKU.

4.7 Psychiatric symptomatology in PKU

As noted above, although both the PKU group and the Control group tended to report more anxiety-related symptoms than depression-related symptoms on the HADS, there was no significant difference between the groups in terms of the number of psychiatric symptoms that they reported. In addition, for the PKU group, there were no significant correlations between participants' blood Phe levels and the number of psychiatric symptoms that they reported. These findings have several implications. First, they suggest that elevated Phe levels did not produce elevated levels of psychiatric symptomatology, as measured by the HADS, in the PKU group. This contrasts with the findings of several previous studies that have suggested that impairments of executive functioning may lead to increased emotional and behavioural problems in children and adults with treated PKU (Fisch et al., 1981; Michals et al., 1985; Realmuto et al., 1986; Ris et al., 1997; Schor, 1983; Smith et al., 1988; Waisbren & Zaff, 1991). The current findings also indicate that the potential stress involved in coping with a chronic disorder

did not produce significant mental health problems in this group, as it has been suggested may occur by Burgard et al. (1994). Finally, the current findings indicate that the significant differences that were observed between the PKU and Control groups on measures of executive functions cannot be attributed to elevated levels of anxiety or depression in the PKU group. For example, it could have been argued that symptoms of anxiety (such as taking excessive care over responses) or depression (such as motor slowing) could have contributed to the PKU participants' slower response times on some of the tests of executive function. However, the results obtained from the HADS do not provide any evidence that this was the case.

4.8 Impact of PKU on everyday life

As noted above, the cognitive deficits shown by the PKU group in this study were fairly subtle. Clinical experience also suggests that the PKU participants did not show any symptoms of executive deficits that were immediately apparent in their everyday lives. However, the extent to which any executive deficits shown by the PKU group impacted on their everyday lives was assessed more formally using the DEX questionnaire. No significant differences between the groups were evident on this measure, either in terms of the participants' ratings of their own behaviour, or in terms of the ratings of their behaviour made by their family and friends. These findings suggest that any cognitive deficit shown by the PKU group was not sufficiently marked to be evident at the gross behavioural level addressed by this questionnaire. As previously noted, the DEX questionnaire measures emotional, motivational, behavioural and cognitive changes that are commonly associated with what has been termed the "dysexecutive syndrome" (Stuss & Benson, 1984; 1986; Wilson, Alderman, Burgess, Emslie & Evans, 1996). Several of the items on the questionnaire would appear to have some

face validity in terms of mapping onto some of the cognitive functions of working memory, response initiation/suppression and selective and sustained attention that were addressed by the tests of executive function used in this study. However, the DEX questionnaire is designed to measure the type of florid dysexecutive symptoms that may be shown by people with structural frontal lesions. A person would therefore have to show quite marked deficits in these areas before those deficits would be detected by the items on the questionnaire. Hence, questionnaire items addressing potential cognitive problems include statements such as "I find it hard to stop repeating, saying or doing things once I've started", and "I find it difficult to keep my mind on something, and am easily distracted". Items addressing potential behavioural problems include statements such as "I act without thinking, doing the first thing that comes to mind", and "I tend to be restless and can't sit still for any length of time". It therefore seems possible that subtle cognitive deficits in the PKU group might have had an impact in their everyday lives, which would not have been detected by this questionnaire.

4.9 Clinical implications of the present findings

Given the high personal and financial costs of maintaining people with PKU on dietary treatment into adulthood, it is important that patients and clinicians have available to them as much information as possible on the cognitive outcome of continuously treated PKU. The results of this study may therefore have important clinical implications in this regard.

The results of this study suggest that there are a number of reasons to be optimistic about cognitive outcome in treated PKU. First, the fact that the PKU participants

achieved a mean IQ score that was in the high average range (corresponding to the 79th percentile of the general population) is encouraging with respect to cognitive outcome in this population with continued treatment. It is also encouraging to note that, despite the fact that the PKU participants had not been able to keep their blood Phe levels within the limits currently recommended by the Medical Research Council, the cognitive deficits that they showed appeared to be less marked than those that have been observed in adults who have discontinued dietary treatment. This observation provides indirect evidence to suggest that there may be benefits to patients of remaining on diet into adulthood. Furthermore, despite the very demanding nature of the prescribed dietary regimen, this study did not produce any evidence to suggest that continuing with dietary treatment placed the PKU group at increased risk of mental health problems, such as anxiety and depression.

However, the fact that, despite continued treatment, there was some evidence that the PKU group showed selective executive deficits relative to controls underlines the importance of taking adult Phe levels seriously. The fact that these deficits were only reflected in increased response times, rather than in increased error rates, might be taken to suggest that these deficits would be unlikely to have important real-life implications. However, there are a number of everyday tasks, such as driving, where it is evident that there could be serious implications if people with PKU had to compromise their response speed in order to maintain the accuracy of their responses. Similarly, patients' ability to function adequately in professions with high-level cognitive demands (such as, for example, air traffic control, train driving or stock trading) might be severely compromised if they were only able to carry out certain executive functions effectively by reducing their response times. It should also be noted that, as the PKU and Control groups in this study were matched on IQ, the results of this study are likely

to provide, if anything, a conservative estimate of the cognitive deficits demonstrated by people with treated PKU.

Another important finding of this study was that, despite the fact that the participants had been identified by their dietician as people who complied well with dietary treatment, their mean blood Phe level was over 800 μmol/l. This finding highlights the difficulty of adhering to the currently recommended limit of 700 μmol/l. The fact that patients find it difficult to remain within the recommended limit is unsurprising given the very demanding nature of the prescribed diet. The necessity of restricting Phe intake means that a wide range of foods must be excluded from the diet or eaten only in strictly controlled quantities. Hence, for example, foods that are naturally high in protein cannot be eaten. Foods which must be excluded from the diet for this reason range from the more obvious examples of high-protein foods such as meat, fish, cheese, eggs, nuts and soya, to ordinary bread, flour, cakes, biscuits and aspartame (found in carbonated drinks). Many other foods that contain some protein, such as potato, milk and cereals, can only be eaten in small, measured quantities. While there are manufactured forms of some staple foods available that are low in protein (such as low protein bread, biscuits, flour and pasta), these can only be obtained on prescription. Another central aspect of the diet is that patients must take special Phe-free protein mixtures, in order to supply essential nutrients that they are unable to obtain from the restricted diet that they must follow. These mixtures (which are very unpleasant-tasting) must be taken regularly with meals and evenly spread out through the day. (This dietary information is taken from a leaflet produced by the National Society for Phenylketonuria, 1998.) It is therefore apparent that this regime is likely to be extremely demanding of patients in terms of time, inconvenience, money and social costs.

Given the very demanding nature of the dietary treatment prescribed for PKU, clinical psychologists may have an important role to play in helping patients to adhere to treatment. Indeed, health psychologists have made important contributions to our knowledge about the factors that influence people's adherence to medical regimens (e.g. Ley, 1988; 1997; Myers & Midence, 1998). Furthermore, health psychologists have helped to identify factors that influence adherence to treatment in another, much more common metabolic disorder, diabetes (e.g. Friedman et al., 1998; TubianaRufi, Moret, Czernichow & Chwalow, 1998). Psychologists have also begun to develop intervention strategies that have been shown to increase levels of adherence in people with diabetes (e.g. Campbell, Redman, Moffitt & Sanson-Fisher, 1996; Greenfield, Kaplan & Warren, 1988). Similar strategies may prove to be useful in helping people with PKU to adhere to their very difficult dietary regime.

4.10 Suggestions for future research

There are many areas in which Clinical Psychologists may be able to make useful contributions to our knowledge about long term outcome in PKU.

First, it is apparent from the present study that the cognitive deficits seen in treated PKU are quite subtle. It would therefore be useful to carry out further studies using more sensitive, timed measures to clarify the nature of these deficits. This could entail the use of computerised tests, rather than pencil and paper tests, as were used in the present study. In particular, it would be important to use timed measures of both functions that are thought to be supported by the prefrontal cortex, and functions that are thought to be supported by more posterior brain regions, in order to make valid comparisons between the two. In particular, the use of timed measures would allow the

contribution of speed-accuracy trade-offs to the performance of both types of test to be assessed.

Second, the fact that few significant correlations were observed between participants' blood Phe concentrations and their cognitive abilities in this study calls into question the nature of the relationship between these variables. As has been noted, evidence from previous studies on the relationship between blood Phe levels and the cognitive deficits observed in treated PKU has also been equivocal. Further research into the mechanisms underlying these deficits is therefore essential, in order to identify the most effective means of minimising them. New technologies, such as MRS, which can be used to scan for chemical compounds (such as Phe) in the brain, may be particularly useful in helping to clarify the relationship between metabolic control and cognitive performance.

The difficulty of making satisfactory comparisons between different cohorts of PKU patients also highlights the importance of carrying out longitudinal studies of the cognitive outcome of treated PKU. As "diet for life" policies are increasingly being implemented around the world, it seems that there will be increasing opportunities for studies of this nature to be carried out.

Finally, it is important to increase our knowledge of the real-life impact of the type of cognitive deficits that were observed in this study. This would help to clarify the extent to which what appear to be quite subtle cognitive deficits have practical implications. This type of information would also give patients and clinicians more meaningful information on which to base their decisions as to whether to continue with dietary treatment.

4.11 Conclusions

The results obtained in this study provide some evidence to suggest that adults with continuously treated PKU show a selective deficit on tasks supported by lateral prefrontal cortex. These results are consistent with the executive deficit hypothesis of treated PKU. It is also important to note that these results were obtained despite the fact that the PKU and Control groups were matched for IQ, meaning that this was a stringent test of the executive deficit hypothesis. The results are also broadly consistent with those that have been obtained in several studies of children with continuously treated PKU. Hence these results do not support the view that the executive deficits that have been observed in children represent a developmental lag, which will disappear with continued treatment. Although it remains an open question as to whether these deficits would be eliminated with better metabolic control than was achieved by the participants in this study, it is questionable how many people would, in fact, be able to remain within the recommended blood Phe limit of 700 μmol/l for life.

Despite the fact that there was some evidence to suggest that the PKU group showed some subtle cognitive deficits, it is encouraging to note that they were able to achieve a mean IQ score that was in the high average range. Furthermore, while it seems that continued treatment was not sufficient to entirely eliminate cognitive deficits in this group, comparisons with results obtained in studies of people who have come off diet provided some evidence to suggest that this group may have benefited from continuing with dietary treatment. However, the fact that few significant correlations were observed between concurrent blood Phe levels and cognitive performance suggests that further research needs to be carried out in order to clarify the mechanisms underlying the cognitive deficits observed in treated PKU. Finally, the results of this

study highlight the difficulty of adhering to the dietary treatment for PKU, and emphasize the importance of developing ways of helping patients to adhere to this regime.

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APPENDICES

Appendix A: Performance on individual subtests of the WASI

	PKU Group	Control Group	t	2-tailed sig.
	Mean (S.D.)	Mean (S.D.)		
Vocabulary[a]	12.20 (2.40)	11.65 (2.60)	0.70	0.49
Similarities[a]	10.95 (1.73)	11.05 (1.93)	-0.17	0.86
Block Design[a]	12.70 (1.92)	13.40 (2.41)	-1.27	0.21
Matrix Reasoning[a]	11.85 (1.87)	11.90 (2.00)	-0.08	0.94
Verbal IQ	108.55 (9.47)	107.20 (10.84)	0.42	0.68
Performance IQ	112.30 (9.68)	114.65 (10.43)	-0.74	0.47

[a] Scaled Score (1-19)

Appendix B: Ethics approval notice

UNIVERSITY COLLEGE LONDON MEDICAL SCHOOL

Administrative Offices
The Rayne Institute
5 University Street
London WC1E 6JJ

Telephone 0171 387 7050
7954
Ext
Fax 0171 383 2462

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

Appendix C: Standard letter written to participants, information sheet, consent forms and advertisement for volunteers

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

Dr. Shelley Channon
Director of Project

Research Assistants: 020-7679-5929
Cristina Cassina
Jasmine Chin
Elaine German
Liz Sinclair

Mr. XXXX

XXXX 2000

Dear Mr. XXXX,

We are 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. Dr. Lee and Dr. Smith from the Metabolic Unit are fully supportive of this work. The study will not influence your clinical management or future care in any way.

Participation in the study involves meeting with one of us (Elaine German) on the same day that you come for your next appointment with Dr. XXXX on XXXX 2000. You will be asked to complete a series of psychological tests which measure aspects of learning, memory and problem-solving. This should take between three and four hours (please see enclosed information sheet for further details). The result will be fed back to you in due course. If you are willing to take part, but cannot make this date, we can make other arrangements.

We will follow up this letter with a telephone call within the next few 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.

Many thanks.

Yours sincerely

Dr. Elaine German
Clinical Psychologist in Training

Dr. Shelley Channon
Senior Lecturer in Psychology, UCL
Head of Neuropsychology Services,
Camden & Islington CHS NHS Trust

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

Researchers: 020-7679-5929

UCL 020-7679-2000
Overseas code +44-20
Fax 020-7916-1989

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 who have conditions which may have involved the brain. This has relevance for everyday living where memory and problem-solving play an important role.

All proposals for research using human subjects 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. The study does not include any blood tests or other medical procedures.

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.

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

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

Research Assistants: 020-7679-5929

UCL 020-7679-2000
Overseas code +44-20
Fax 020-7916-1989

CONSENT FORM

Memory and problem-solving study

Director of project: Dr. Shelley Channon

To be completed by the volunteer:	**Delete as necessary:**
Have you read the information sheet about this study?	Yes/No
Have you had an opportunity to ask questions and discuss this study?	Yes/No
Have you received satisfactory answers to all your questions?	Yes/No
Have you received enough information about this study?	Yes/No
Which researcher have you spoken to about this study?	.....
Do you understand that you are free to withdraw from this study at any time, and without giving a reason for withdrawing?	Yes/No
Do you agree to take part in this study?	Yes/No

Signature of volunteer .....
Name .....
Date .....
Address .....
.....
.....
.....

Signature of researcher .....
Name .....
Date .....

Subdepartment of Clinical Health Psychology
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CONSENT FORM

Memory and problem-solving study

Director of project: Dr. Shelley Channon

To be completed by the volunteer:	**Delete as necessary:**
Have you read the information sheet about this study?	Yes/No
Have you had an opportunity to ask questions and discuss this study?	Yes/No
Have you received satisfactory answers to all your questions?	Yes/No
Have you received enough information about this study?	Yes/No
Which researcher have you spoken to about this study?	.....
Do you understand that you are free to withdraw from this study at any time, without giving a reason for withdrawing, and without affecting your future medical care?	Yes/No
Do you agree to take part in this study?	Yes/No

Signature of volunteer .....
Name .....
Date .....
Address .....
.....
.....
.....

Signature of researcher .....
Name .....
Date .....

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

Notice for Undergraduates/Graduates

Volunteers are needed to participate in a study on memory and problem solving for a payment of **£15**

The study will look at how people remember and solve problems and will involve filling in some questionnaires, carrying out tests of memory, and problem solving, and a brief interview. You will not be required to give any physical tests, such as giving a blood sample.

We need people aged 18-30 years in good mental and physical health who do not have any history of accident or illness affecting the brain.

If you are interested in helping with our research, please telephone 020 XXXX XXXX and ask for XXX at UCL, 1-19 Torrington Place, London, or email us at: XXXX.

We look forward to hearing from you.

Acknowledgements

First, I would like to thank Dr Shelley Channon, for her excellent supervision of this research project. I would also like to thank Dr Philip Lee, Consultant in Metabolic Medicine, and Ms Maggie Lilburn, Metabolic Dietician, whose help and support to me in carrying out this research were invaluable. I am also grateful to the patients of the Metabolic Unit who took part in the study, for giving so generously of their time. Finally I would like to thank my husband, family and friends for their continued support and encouragement.

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