

LUCY J.B. TINNING BSc

# COGNITIVE FUNCTIONING AND HEALTH RELATED QUALITY OF LIFE IN PATIENTS WITH PRIMARY ANTIPHOSPHOLIPID SYNDROME

**Section A:**

Cognitive Functioning and Health Related Quality of Life in Patients with Primary Antiphospholipid Syndrome: A Review of the Literature

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**Section B:**

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# DECLARATION FOR MAJOR RESEARCH PROJECT

**DECLARATION**

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

Signed …….…..... (candidate)

Date .....

**STATEMENT 1**

This thesis is the result of my own investigations, except where otherwise stated. Other sources are acknowledged by footnotes giving explicit references. A bibliography is appended.

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I hereby give consent for my thesis, if accepted, to be available for photocopying and for inter-library loan, and for the title and abstract to be made available to outside organisations.

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## Summary

**Section A:** Cognitive Functioning and Health Related Quality of Life in Patients with Primary Antiphospholipid Syndrome

This paper reviews the literature surrounding cognitive functioning in patients with Antiphospholipid syndrome (APS) in the context of quality of life as an indicator of adaptation to chronic illness. The review focuses on cognitive functioning in APS patients and related clinical populations, describing and critiquing the empirical research literature exploring the evidence for cognitive deficits in these populations. Psychological theories of adaptation to chronic illness are discussed in relation to the concept of quality of life and research examining the relationship between cognitive dysfunction in APS and related clinical populations and health- related quality of life (HRQoL) is summarised. The limitations of previous research examining these factors are highlighted, demonstrating the need for empirical studies that address cognitive functioning and quality of life in patients with primary APS (PAPS).

**Section B:** The Relationship of Cognitive Functioning and Health Related Quality of Life in Patients with Primary Antiphospholipid Syndrome

This study investigated the relationship between cognitive functioning and HRQoL in patients with PAPS. A cross-sectional design was used. Participants were recruited from a large London medical centre where assessment involved the completion of a questionnaire measuring HRQoL and a comprehensive battery of neuropsychological tests of general intelligence, memory and executive functioning.

**Section C:** Critical Appraisal

The critical review is structured to address four specific questions providing a reflective account of how the involvement in this project has contributed to the researcher's skills and abilities and highlighted areas where further learning is necessary. The review also discusses further clinical applications and research for cognitive functioning and HRQoL in patients with PAPS.

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**Section A**

# Cognitive Functioning and Health Related Quality of Life in Patients with Primary Antiphospholipid Syndrome: A Review of the Literature

Lucy JB Tinning

Canterbury Christ Church University

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**Abstract**

Antiphospholipid syndrome (APS) is an autoimmune disease and chronic illness characterised by thrombosis and recurrent pregnancy morbidity. It may occur as an isolated diagnosis, primary APS (PAPS), or it may be secondary, associated with other autoimmune disorders. A clinical feature of APS is cognitive dysfunction which may be a direct manifestation of central nervous system involvement. It may also be a secondary response to a diagnosis of a life-altering chronic illness. The psychosocial process of adapting to a chronic illness has become an important measure in health outcomes which relate specifically to health related quality of life (HRQoL). This review evaluates the literature on cognitive dysfunction and HRQoL in APS and demonstrates the need for further empirical research in this clinical population to inform the development of treatment approaches and health outcomes for those with APS. Where PAPS is considered the pure form of the disease, future research should endeavour to include this specific group.

## 1. OVERVIEW

Antiphospholipid Syndrome (APS) is a recently described autoimmune disorder with a vast range of clinical features. While progress has been made in terms of the science of the disease (Lockshin, 2006) and recognition of the condition has grown, health professionals in general are still largely unaware of it (Donnan & McDonald, 2009) and there remain many unanswered questions (Lockshin, 2006). Pharmacological interventions to treat and manage the symptoms of APS are established; however, the social, psychological and emotional experience of this illness, like many chronic illnesses, is important to consider in relation to health outcomes. Although poorly recognised and relatively unexplored (Gordon, Goldenberg, Erkan, & Lockshin, 2009; Pattanaik & Brey, 2006), one clinical manifestation of this disease, which may influence these experiences, is cognitive functioning.

## 2. OBJECTIVES

The purpose of this literature review is to explore cognitive functioning in APS patients in the context of quality of life as an indicator of adaptation to chronic illness. The review will follow a structure as follows: i) Clinical features of APS will be described, with a specific focus on cognitive functioning in APS patients and related clinical populations, ii) Empirical research literature exploring the evidence for cognitive deficits in these populations will be described and critiqued, iii) Psychological theories of adaptation to chronic illness will then be discussed in relation to the concept of quality of life, iv) Research examining the relationship between cognitive dysfunction in APS and related clinical populations and health-related quality of life will be summarised. Within this context, the limitations of previous research examining these factors will be highlighted, demonstrating the need for empirical studies that address cognitive functioning and quality of life in patients with APS.

## 3. METHOD

The literature was searched in 2010 and 2011 using electronic databases to search for research articles published between 1980 and 2011. Details of the method including the selection procedure can be found in Appendix A.

## 4. REVIEW

### 4.1 Antiphospholipid Syndrome: An Autoimmune Disease and Chronic Illness

#### *4.4.1. Definition and clinical manifestations*

Antiphospholipid syndrome (APS), also known as Hughes' syndrome was first recognised 26 years ago. APS is an autoimmune disease and is a prothrombotic condition. It is diagnosed on the basis of clinical and laboratory findings. There must be a presence of clinical event/s including venous/arterial thrombosis and/or pregnancy losses in association with laboratory blood tests confirming moderate-to-high titer antiphospholipid (aPL) antibodies (Miyakis et al., 2006). APS may occur as an isolated diagnosis (primary APS; PAPS) or it may be secondary. It is secondary where individuals with other autoimmune disorders also have moderate-to-high titre aPL antibodies and/or the presence of the lupus anticoagulant. There is a high prevalence of APS among patients with Systemic lupus erythematosus (SLE) – also referred to as SLE-related APS (Tektonidou, Varsou, Kotoulas, Antoniou, & Moutsopoulos, 2006).

The clinical spectrum of APS features is extensive (D'Cruz, 2006) and there are no significant differences in the main clinical features whether the syndrome is primary (PAPS) or secondary (Vincent & Mackworth-Young, 2006). Clinical associations include: gastrointestinal, vascular disease, skin, bone, obstetric, renal, pulmonary, endocrine and haematological. Central Nervous System (CNS) involvement is one of the most common features of APS including neuropsychiatric manifestations such as stroke, seizures, cognitive dysfunction, migraine, transient ischaemic attack, chorea, psychosis, multiple-sclerosis (MS) like features, sensorineural hearing loss and mood disorders. Although common, not all patients with primary or secondary APS experience CNS involvement.

Where PAPS and secondary APS are characterised by the presence of moderate-to-high aPL antibodies, they can be present at low levels with an absence of clinical events (thrombosis and pregnancy losses) and therefore asymptomatic patients testing positive for aPL antibodies do exist. However, these patients can experience some of the neuropsychiatric syndromes that those with definite primary and secondary APS experience such as seizures, chorea, migraine and cognitive dysfunction (Erkan, Kozora, & Lockshin, 2011).

*4.1.2. Prevalence of APS*

The prevalence of aPL antibodies in otherwise healthy populations is less than 1% and up to 5% in older healthy populations and the prevalence increases with age (D'Cruz, 2006). At least twice as many women as men develop APS. This parallels other autoimmune connective-tissue diseases which have a female predominance. It is difficult to measure the number of people with APS. Studies indicate that between 5-40% of individuals with thrombosis and no history of SLE have aPL antibodies. Additional studies suggest that aPL

antibodies play a role in approximately 20% of strokes in individuals under the age of 40 (Khamashta, 2006). Up to 30% of patients with SLE have aPL antibodies (D'Cruz, 2006).

#### *4.1.3. Diagnosis of APS*

APS is recognised as a common disorder and once diagnosed, is treatable. However, for many patients diagnosis is often delayed, sometimes for years, with consequent disability, loss of livelihood, inability to start a family or even death (D'Cruz, 2006). APS is often not defined until a clinical event has occurred, usually thrombosis (Vincent & Mackworth-Young, 2006). Donnan and McDonald (2009) found that the median pre-diagnosis period for patients was 3 years. The most common diagnoses given were migraines (18.6%) and MS (12.7%). Other common diagnoses were miscarriages, SLE, stress, depression and anxiety.

### **4.2. Cognitive Dysfunction: A Clinical Manifestation of APS**

#### *4.2.1. Cognitive dysfunction in APS: overview*

Cognitive deficits associated with secondary APS and PAPS can vary from mild neurocognitive disorders to severe global dysfunction in the context of dementia. Although interest in this area has increased in recent years, research is limited and few formal neuropsychological studies have been conducted to assess the prevalence and nature of cognitive deficits in patients with APS (Pattanaik & Brey, 2006). Studies evaluating neurocognitive deficits have mainly included SLE patients testing positive for aPL antibodies (low aPL levels and no clinical events thereby not meeting criteria for APS). Research distinguishing secondary APS and PAPS patients specifically is more limited and mainly

anecdotal (Pattanaik & Brey, 2006). Findings so far have not identified any consistent pattern of cognitive dysfunction although there are similarities in the deficits found. When cognitive dysfunction is mild, patients complain of deficits in attention, difficulty concentrating on tasks, forgetfulness and other deficits that mildly interfere with everyday function. These less severe forms of cognitive impairment are considered common in patients with APS and may be the only clinical manifestation of APS being present independently of CNS involvement (Denburg, Carbotte, Ginsberg, & Denburg, 1997).

The recognition of the subtle forms of cognitive dysfunction that may not have been identified by brief examination has been greatly facilitated by the application of neuropsychological assessment. Furthermore, neuropsychological tests have been sensitive enough to measure deficits in patients without any history of neuropsychiatric or CNS involvement e.g. stroke. This has improved understanding about the nature of cognitive impairment in patients with APS, as well as the involvement of aPL antibodies on the CNS (Tektonidou, et al., 2006) and their ability to compromise it (Sanna, 2006).

*4.2.2. Cognitive dysfunction in APS and the role of psychological distress*

Emotional and psychological distress is common in patients with chronic diseases (Harrison & Ravdin, 2002) and is known to influence reports of cognitive functioning as well as performance on neuropsychological tests (Sweet, Newman, & Bell, 1992). The role of such variables has not been explored in patients with APS but it has been explored in relation to cognitive functioning in patients with SLE. The issue is complicated by controversy as to whether psychological factors, in particular, depression, are a direct manifestation of CNS

involvement or a secondary response to a chronic illness (Denburg, Carbotte, & Denburg, 1987).

In either instance, performance on neuropsychological tests may be affected. Some researchers argue that due to the high prevalence of distress in those with SLE, cognitive deficits can be attributed to the psychological factors of living with a chronic disease (Hutchinson, Nehall, & Simeon, 1996). However this is not supported by some studies exploring depressive symptoms in SLE patients and other chronic illnesses (Kozora, Thompson, West, & Kotzin, 1986). Kozora et al's (1986) study demonstrated no relationship between the cognitive aspects of depression and neuropsychological test performance. This is supported by earlier research, also indicating no relationship between cognitive function in patients with SLE (including neuropsychiatric patients) and psychological distress (Carbotte, Denburg, & Denburg, 1986; Denburg et al., 1997; Glanz et al., 1997; Waterloo, Omdal, Mellgren, & Husby, 1997).

Monastero et al. (2001), however, did find a significant relationship between depression and cognitive dysfunction in SLE patients with and without overt neuropsychiatric manifestations of disease compared with age-matched healthy controls. Post hoc analyses showed that the neuropsychiatric SLE patients performed more poorly than SLE patients without neuropsychiatric involvement, and both patient groups performed worse than controls. However, only the neuropsychiatric SLE patients differed significantly from the controls on measures of depression and anxiety. Multivariate analyses found that depression was the only clinical variable that predicted cognitive test performance. Closer analysis of the data revealed that despite the statistically significant differences in psychological symptoms, the group means on the anxiety and depression scales were not clinically significant. Thus,

although the neuropsychiatric SLE group reported a greater number of symptoms consistent with depression, they were not clinically depressed. This uncertainty and debate as to whether emotional and psychological disturbances in SLE reflect CNS involvement or a reaction to a chronic illness has informed research exploring cognitive dysfunction in patients testing positive for antiphospholipid antibodies, SLE-related APS and Primary APS.

## 4.3. APS and Cognitive Dysfunction: The Evidence Base

### *4.3.1. Cognitive dysfunction, antiphospholipid (aPL) antibodies and Systemic lupus erythematosus*

Studies of SLE patients with aPL antibodies have shown that the antibodies may play a primary role in the pathogenesis of cognitive impairment and that the application of neuropsychological assessments has a use in detecting early neuropsychiatric involvement in these patients. Maeshima,Yamada, Yukawa and Nomoto (1992) reported that 72% of SLE patients (n = 21) with aPL antibodies demonstrated abnormal neuropsychological findings in visuoconstructive skills and verbal learning. This study did not include any measures of depression or emotional distress. Denburg, Carbotte, Ginsberg and Denburg (1997) revealed a significant association between SLE patients testing positive for aPL antibodies and cognitive impairment. These patients scored significantly lower than healthy controls (effect size range = .52 to 1.24) on most measures and SLE patients that tested negative for aPL antibodies (effect size range = .42 to .79) on measures of verbal memory, cognitive flexibility and psychomotor speed. Furthermore, aPL positive patients were found to be two to three times more impaired than aPL negative patients. There was no significant relationship with cognitive impairment and emotional distress. Of note is that subsequent analysis of subjects

from this study that did not have neuropsychiatric disease (CNS involvement) produced similar results. In another study by Leritz et al. (2002) including aPL antibody patients without CNS involvement, aPL positive patients (n=29) performed significantly worse than aPL negative patients (n = 27) on measures of neuropsychological functioning including attention, concentration, visual search, spatial learning and memory. No clear pattern of cognitive impairment emerged. Of importance was the finding that when the influence of depression was removed statistically, the aPL positive group still performed worse indicating that observed deficits were not necessarily a manifestation of depressive symptoms. This study was weakened by considerable attrition rates in both groups, although there were no differences between groups (Leritz et al., 2002).

The studies described have relied mainly on one-time assessment and so do not consider influence of aPL antibodies as they fluctuate. The relationship between aPL antibody levels and neuropsychological functioning has been examined in longitudinal studies by several researchers with varying results. Hanly, Hong, Smith and Fisk (1999) classified groups of SLE patients with and without CNS involvement as cognitively impaired or unimpaired and examined changes on neurological assessment performance in relation to aPL status over five years. Patients testing positive for aPL antibodies demonstrated significantly greater decline in the areas of conceptual reasoning and executive ability. Those with persistently elevated aPL levels performed worse over time on tasks of psychomotor speed. Another longitudinal study (Menon, et al., 1999) reported an association between aPL levels and cognitive functioning in SLE patients assessed on two occasions separated by 12 to 18 months. Patients with persistently elevated aPL levels performed more poorly on areas of verbal fluency, concentration, attention and reaction time. No significant relationship between cognitive functioning and actual antibody level was found. However, the reliability of the

study was of concern due to the small sample and the exclusion of any measure for low mood or distress.

*4.3.2. Cognitive dysfunction in Primary APS and SLE-related APS*

Among studies that have included patients with a diagnosis of definite APS, most have focused on dementia or cognitive decline in an aging population but have not provided data on the subtle forms of cognitive dysfunction (Gomez-Puerta et al., 2005; Asherson et al., 1987; Inzelberg, Bornstein, Reider, & Korczyn, 1992) . Chapman, et al. (2002) identified a high frequency of dementia in PAPS patients using a screening tool and standard clinical criteria. Fifty six percent of APS patients had dementia based on diagnostic criteria (demented APS patients mean age = 68 compared to non-demented APS patients mean age = 51). However, standardised cognitive tests were not used.

In studies which have explored the presence of less severe cognitive dysfunction with neuropsychological measures, sample sizes have been small. Aharon-Peretz et al. (1995) used a comprehensive battery of neuropsychological tests to examine 20 patients with PAPS (14 with CNS involvement) and 10 healthy controls. Thirteen of the 14 patients with CNS disease had mild cognitive deficits. These included: impaired attention, semantic fluency, memory and visuospatial functions and slowing of thought process. Aharon-Peretz et al. (1995) did not include measures of emotional and or psychological distress and three participants had an affective disorder and three met diagnostic criteria for schizophrenia. Mikdashi and Kay (1996) described 4 PAPS patients (without CNS involvement) with impairment in visual attention, executive function abilities and impairment in verbal and non verbal-memory skills. In an unpublished pilot study comparing 13 PAPS patients with SLE patients with aPL

antibodies matched for gender, age, education and IQ, results indicated lower mean scores for PAPS patients on ten neuropsychological tests, performance on two of the tests was significant (Harrison & Ravdin, 2006).

Tektonidou et al. (2006) examined patients with PAPS (n = 39), SLE-related APS (n = 21), healthy controls (n = 60) and disease controls (n = 25; 15 patients with SLE and 10 patients with rheumatoid arthritis) using a neuropsychological battery measuring learning and memory, attention, executive functions and visuospatial skills and depression. The findings indicated that 42% of the 60 patients with APS and SLE-related APS (combined) had cognitive deficits compared with 18% of healthy controls ($p = .005$). Deficits were common in verbal fluency and complex attention. There was no difference in cognitive performance between PAPS patients and SLE-related APS patients or the disease and healthy controls groups. This study used a comprehensive battery of neuropsychological tests and having a disease control group strengthened the methodology. However, the small sample size has implications for power in detecting modest differences. Mild and severe depression was reported in 5% of the APS group (combined); no details of how this was measured were given.

Finally, Jacobson, Rapport, Keenan, Coleman and Tietjen (1999) conducted a study with subjects without an autoimmune disease, neurological disease (CNS involvement) or psychiatric history (including depression) but who tested positive for aPL antibodies. The findings demonstrated significant differences from a matched control group on measures of memory, executive functioning, verbal learning and visuospatial skills. There were no significant associations between cognitive impairment and depression.

In summary, there are a limited number of empirical investigations examining the cognitive dysfunction in patients with PAPS; most focus on the role of aPL antibodies in patients with SLE-related APS. Neuropsychological assessments have been useful in identifying cognitive impairment in these populations. The research reviewed reveals that aPL antibodies in those with and without an autoimmune disease diagnosis of PAPS or SLE-related APS, regardless of CNS involvement, are not likely a cause of global cognitive dysfunction but that any relationship that exists between these antibodies and cognition is complicated. Studies that were methodologically more robust considered moderator variables such as psychological and emotional distress and demonstrated that cognitive deficits may not always be associated with such factors.

## 4.4. APS: A Chronic Illness - Quality of Life and Psychosocial Adaptation

### *4.4.1. Chronic illness and quality of life*

APS is a chronic illness meaning it involves a disease of a long-lasting nature without a prospect of cure, characterised by a progressive course (de Ridder, 2004). Being diagnosed with a chronic illness has the potential to induce profound changes in a person's life resulting in serious negative effects on quality of life (Dimond, 1984). Quality of life refers to a broad set of concepts such as well-being, satisfaction, happiness and functionality as well as financial and environmental factors (de Ridder, 2004). More specifically, in the context of chronic illness it considers that individuals may be faced with significant changes in their life roles and social and familial relationships while concurrently managing psychological distress, physical pain, prolonged medical treatment and interference or restriction in activities related to daily living (Charmaz, 1983; Livneh & Antonak, 1997). The way in which

people navigate the process of adapting to these life changes from the onset of chronic illness has been an important concept in research (Brennan, 2001).

*4.4.2. Psychosocial adaptation to chronic illness: psychological models*

At a fundamental level, adaptation may be conceived as a process of responding to the functional, psychological and social changes that occur with the onset and experience of living with a disability and/or chronic illness (Bishop, 2005). Psychological studies on adaptation to chronic illness are guided by models of stress and coping, focusing on the role of stress and moderators of stress at onset and during the course of illness. These models derive from general frameworks regarding adaptation to stressful experiences, highlighting the role of stressors as possibly affecting health outcomes, well-being and adjustment (Cohen & Lazarus, 1979).

Lazarus and Folkman's (1984) transactional cognitive-phenomenological theory postulates that the impact of stress, such as the diagnosis of a chronic illness, is mediated by cognitive appraisals of the illness and the personal and social resources available to assist coping with it. Individuals adapt to illness by applying coping strategies that are appropriate to the situation. These coping strategies are either problem-focused, to alter person-environment relationships, which are appropriate when the stressor is deemed changeable and emotion-focused coping strategies to regulate internal states, appropriate where the stressor is unchangeable.

A later model, proposed by Livneh and Antonak (1997) suggested that four groups of variables influence adaptation outcomes including disability-related variables,

sociodemographic factors, personality attributes (locus of control, coping strategies) and social and environmental factors. This interactive model is more congruent with the concept of psychosocial adaptation being a complex and individual process (Larson & Lubkin, 2009).

A more recent interactive framework related to adaptation includes Moos and Holahan's (2007) conceptual model of the determinants of health related outcomes of chronic health and disability. The model conceptualises coping and integrates it into a broader model which proposes five sets of factors that are associated with the selection of appropriate coping skills and resulting health outcomes such as adaptation. Included are three factors that influence cognitive appraisal: 1) personal resources, 2) health-related factors and 3) social and physical context. An individual's cognitive appraisal dictates what adaptation tasks need to be accomplished. These adaptation tasks include: managing symptoms, treatment and emotions, forming relationships with healthcare providers, maintaining a positive self image, relating to family members and friends and preparing for an uncertain future. The three factors influencing cognitive appraisal and the cognitive appraisal itself then mediates the choice of coping skills leading to the outcome of adaptation. The categories of coping skills identified by Moos and Holahan (2007) include: logical analysis and the search for meaning, positive reappraisal, seeking guidance and support, taking problem-solving action, cognitive avoidance or denial, acceptance and resignation, seeking alternative rewards and emotional discharge.

Points of consensus that have emerged across theories include the notions that adaptation to the onset of chronic illness is a highly subjective, unique and complex multidimensional process, sensitive to the environment and its demands and resources, and to

personality traits that influence the appraisal of illness, and the resources for coping (Bishop, 2005; de Ridder, 2004; Folkman & Moskowitz, 2004).

#### *4.4.3. Quality of life: an indicator of adaptation*

Because adaptation is multidimensional, it is suggested that an appropriate measure of adaptation to chronic illness is one that a) is sufficiently broad to assess change across a range of life domains and b) is able to portray the individual's subjective experience of changes within those domains (Bishop, 2005). As quality of life represents an appropriate framework for defining and understanding the adaptation process, quality of life measures are considered most likely to tap into broad dimensions of a person's representations of their physical and social world (Brennan, 2001).

### 4.5. Quality of Life (QoL), Health Related Quality of Life (HRQoL) and Cognitive Dysfunction

#### *4.5.1. QoL and HRQoL*

Primary outcomes in health care were traditionally focused on mortality and morbidity. However, identifying the impact of interventions and describing and characterising the patient's experience of medical care through quality of life (QoL) assessments in health settings is now common (McGee, 2004).

Definitions of QoL proliferate ranging from philosophical statements to pragmatic definitions, developed to assist operationalising the concept (McGee, 2004). QoL as a concept

is regarded as broad and within it are included concepts such as well-being, satisfaction, happiness, expectancy, or functionality as well as financial and environmental factors. The concept of Health Related Quality of Life (HRQoL) has been adopted to focus primarily on medical aspects and has developed from the idea that where health interventions address health-related aspects of an individual's life, they should be evaluated against HRQoL parameters. HRQoL as a separate concept from QoL has been defined by Revicki et al. (2000) as, *"The subjective assessment of the impact of disease and treatment across the physical, psychological social and somatic domains of functioning and well-being" (p.888).*

Much research exploring quality of life in patients with chronic illness relates to HRQoL, referring to quality of life aspects specific to an individual's health. Physical, social and role functioning and mental and general health are included in most conceptualisations of HRQoL. Concepts of vitality, pain and neurocognitive functioning are generally subsumed under these broader domains (Ware, 1987). The term HRQoL will be adopted hereon in this review.

*4.5.2. HRQoL in PAPS*

No research exploring the illness experience of patients with PAPS through HRQoL measures could be found at the time of this review. However, there has been one small scale study (N=10) by Erkan, Yazici, Sobel and Lockshin (2000) investigating long-term functional outcome (after 10 years) of APS patients experiencing various clinical symptoms of APS. Eight patients with organ damage were unable to perform everyday activities important to their quality of life (functionally impaired). Causes of functional impairment were cognitive dysfunction, cardiovascular disease, aphasia and expressive aphasia.

Research that has adopted HRQoL measures with patients with other autoimmune diseases such as SLE has been extensive and findings indicate that scores on HRQoL measures in this population have been 30-40% lower than those reported by matched peers (Sweet, Doninger, Zee, & Wagner, 2004). All domains of HRQoL appear to be affected by SLE (Fortin, et al., 1998; Gladman, Urowitz, Ong, Gough, & Mackinnon, 1996; Wang, Mayo, & Fortin, 2001) and domains most affected include subscales assessing general health, vitality, physical functioning, roles physical and roles emotional.

## 4.6. Cognitive Dysfunction and HRQoL in PAPS and Other Chronic Illnesses

### *4.6.1. Cognitive dysfunction and HRQoL in PAPS*

Research focussing specifically on the relationship between cognitive functioning and HRQoL in patients with PAPS could not be found at the time of this review.

Studies which highlight important considerations for PAPS patients include those with other clinical populations such as patients with SLE and patients with neurological conditions.

### *4.6.2. Cognitive dysfunction and HRQoL in SLE*

There is a paucity of studies exploring cognitive dysfunction and HRQoL with SLE patients. The most recent and most well described study is that of Tam et al. (2008). This included a sample of 291 Chinese SLE patients. Validated measures were employed to ascertain the association of neuropsychiatric manifestations, including cognitive functioning, depression and anxiety, and HRQoL. Measures of cognitive functioning were intended to

identify impairments in memory and language and executive functioning and included Chinese versions of the Mini-Mental State Examination (MMSE) and the Mattis Dementia Rating Scale – Initial/Preservation (CDRS-IP) subscale. Anxiety and Depression were measured with the Hospital Anxiety and Depressions Scale (HADS) and the Medical Outcomes Survey Short Form-36 (SF-36) was used to measure HRQoL. Findings demonstrated that cognitive impairments of executive functioning as measured by the CDRS-IP were associated with impairment of the mental health subscale of the SF-36. Of note was the finding that the HADS depression score was the only independent explanatory variable associated with impairment of all subscales of SF-36, which measures both physical and mental health functions. The HADS anxiety score was associated with four mental health subscales. Anxiety and depression were not significantly associated with any other demographic or clinical variables.

Tam et al. (2008) acknowledge that the measures used to identify cognitive impairment are not necessarily sensitive enough for more mild cognitive deficits, such as those reported in patients with APS.

Hanly, Cassell and Fisk (1997) incorporated a comprehensive battery of neuropsychological measures which included the WAIS-R and WMS-R, in a longitudinal study exploring cognitive functioning in patients with SLE over a five year period. Patients were assessed at three time points. HRQoL was measured with the SF-36 at the final time point. No significant differences were found between patients who displayed cognitive impairment (n = 7) and those who did not (n = 53).

Where occupational status is one objective measure of global functioning that correlates with QoL ratings in a variety of medical disorders there are studies that have focused on employment (Panopalis et al., 2007; Utset, Fink, & Doninger, 2006). Utset et al. (2006) demonstrated the specific influence of cognitive impairment on work status in 50 SLE patients. Patients were assessed for work status, disease characteristics, fatigue, anxiety, depressive symptoms, HRQoL and neuropsychological performance. Extensive neuropsychological assessments included a range of measures for pre-morbid verbal IQ, verbal and visual memory, attention/processing speed, working memory, language function,. motor speed and HRQoL. Fifty percent of patients had cognitive impairment. Of these, 32% had obtained formal work disability, 16% had self-report work disability and 52% denied having work disability. Subjects with self-reported work disability were more likely to have neurocognitive dysfunction and poor quality of life.

Panopalis et al. (2007) assessed the contribution of memory impairment to employment status in 832 patients with SLE. After adjusting for covariates such as disease duration, disease activity, education level, depressive symptoms and demographic variables, those with mild-moderately or severely impaired memory experienced greater work disability than those with intact memory function. There was also a strong correlation between depressive symptoms and memory impairment. Depressive symptoms were found to be a strong predictor of employment and inability to work. Even mild memory impairment interfered with work as key aspect of quality of life.

*4.6.3. Cognitive dysfunction and HRQoL in neurological conditions*

Studies in neurological conditions demonstrate that cognitive impairment is a strong predictor of quality of life (Mitchell, Kemp, Benito-Leon & Reuber, 2010; Mitchell, Benito-

Leon, Gonzales & Rivera-Navarro, 2005). Historically, these studies have focused on dementia and severe cognitive impairment but recently, there has been an increasing recognition of a broad spectrum of impairment including subclinical or mild cognitive impairment (Mitchell et al., 2010). Research has revealed that mild impairment with specific deficits such as inattention, dysexecutive function and processing speed may influence ability to work, interpersonal relationships and leisure activities. This research is summarised below.

Compared with healthy controls, patients with brain tumours demonstrate significant reductions in information processing speed, psychomotor function, verbal and working memory, executive functioning and HRQoL (Klein et al., 2003). Subtle deficits were found to prevent some brain tumour survivors from returning to pre-morbid autonomy and occupations (Giovagnoli & Boiardi, 1994).

In stroke patients, Hochstenbach, Anderson, Van Limbeck, & Mulder, (2003) employed a comprehensive battery of neuropsychological tests and found HRQoL to be associated with deficits in spatio-temporal and or/sequential aspect of behaviour. Poor HRQoL was more likely if patients had a poor result on the Trail Making Test B. Kuahanen et al. (2000) found that infarct volume, aphasia, impaired motor and cognitive function were linked to poorer QoL however, depression was the most significant.

Occupational status is an objective measure of global functioning that also correlates with QoL ratings in head injury (Mitchell et al., 2010). Even In mild traumatic brain injury, verbal memory, verbal fluency and speed test of planning and strategy are predictive of work status 3-15 months later. Many studies with patients with MS demonstrate an association between cognitive deficits and lowered HRQoL (Amato, Ponziani, Siracusa, & Sorbi, 2001;

Cutajar et al., 2000; Gold, Schulz, Monch, Shulz, & Heesen, 2003; Shawaryn, Schiaffino, Larocca, & Johnston, 2002) including memory impairment and executive function and information processing. Mitchell et al., 2006 examined all degrees of cognitive impairment using a neuropsychological testing as well as the Clock Drawing Test and MMSE screening instruments. After controlling for depression, comprehensive ratings of cognition contributed to poor HRQoL.

While there have been no studies including patients with PAPS or SLE-related APS, overall, there is empirical evidence demonstrating that cognitive dysfunction, from mild to severe, in chronic illnesses and neurological conditions is associated with poor HRQoL, even when depression is controlled for. The implications on a direct level therefore, are that cognitive dysfunction influences physical, psychological and social domains of functioning and well-being which may relate to adaptation and coping with illness and disability.

## 5. FUTURE DIRECTIONS AND IMPLICATIONS

Primary APS is a chronic illness with many clinical features including cognitive dysfunction ranging from mild to severe. This review has focused on this clinical manifestation because it remains poorly recognised (Gordon, Goldenberg, Erkan, & Lockshin, 2009; Pattanaik & Brey, 2006), with few studies utilising sensitive neuropsychological measures to assess the prevalence and nature of these deficits (Pattanaik & Brey, 2006). Although PAPS is the pure form of APS, it is this group about whom the least is known (Vincent & Mackworth-Young, 2006). The studies presented in this review have included SLE patients testing positive for aPL antibodies as it is this population that closely resembles that of PAPS. These studies, therefore, contribute to knowledge and inform future research in

this clinical population. The findings demonstrate cognitive deficits in groups with and without CNS involvement of the disease in a variety of domains including: attention, semantic fluency, memory, visuospatial functions, executive functioning and psychomotor speed. It is recognised that some impairments in this population are so mild such that they are not easily recognised by measures of cognitive functioning. Furthermore there appears to be no specific pattern in the cognitive deficits of this group. These findings suggest the necessity for the utilisation of a comprehensive battery of sensitive well validated and reliable neuropsychological measures in future studies. Furthermore, while some studies found emotional and psychological distress had no association with cognitive dysfunction, the role of these variables remains unclear; as such, future research may also control for these variables to add further rigour to research design.

In focusing on cognitive dysfunction, this review has highlighted the influence that this clinical feature may have on a patient's HRQoL, an important measure of health outcomes. HRQoL relates to the adaptation to functional, psychological and social changes experienced by some patients with a diagnosis of a chronic illness. This review has demonstrated that there is also a paucity of research investigating HRQoL outcomes with this clinical population. Research exploring this multi-dimensional concept in similar chronic illnesses has been presented, because, again, it can contribute to our knowledge about quality of life as an indicator of adaptation in patients with PAPS and inform the design of future empirical investigations with this population. The studies presented highlighted the relationship between cognitive deficits and poor HRQoL suggesting that patients may struggle to adapt and cope with this clinical feature specifically. As there has been no research exploring this experience in PAPS, it is recommended that future studies address this gap in knowledge as it may contribute to significantly influencing health outcomes for patients.

It is expected that the number of patients with APS and the number recognised as having APS will grow (Kasthuri & Roubey, 2009). Therefore a better understanding of the nature of cognitive dysfunction in PAPS patients and the influence this has on quality of life is theoretically and clinically important in informing the development of treatment approaches. There may be a role for health professionals, such as clinical health psychologists, to monitor cognitive functioning in this clinical population and to intervene where patients are having difficulties adapting to the condition. Advancing the understanding of PAPS should facilitate the development of improved treatment and outlook for patients with all forms of APS (Vincent & Mackworth-Young, 2006).

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**Section B**

# The Relationship of Cognitive Functioning and Health Related Quality of Life in Patients with Primary Antiphospholipid Syndrome: A Pilot Study

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## Abstract

**Objective**: To explore the relationship between cognitive functioning and health related quality of life (HRQoL) in patients with Primary Antiphospholipid Syndrome (PAPS).

**Method:** Cross sectional comparisons of PAPS patients (PAPS thrombosis; *n* = 15; PAPS pregnancy; *n* = 15) and healthy controls (*n* = 15) on a battery of neuropsychological assessments and a measure of HRQoL.

**Results:** PAPS thrombosis patients were twice as likely to be designated as cognitively impaired compared to PAPS pregnancy patients. PAPS thrombosis patients demonstrated lower performance on measures of memory and executive functioning compared to controls. PAPS pregnancy patients also performed more poorly on these measures compared to controls although not significantly. Both groups demonstrated poor HRQoL across physical and mental subscales. Both groups were significantly more impaired in all physical domains and one mental domain of HRQoL compared to controls. Neuropsychological outcomes in general intellectual abilities, memory and executive functioning were significantly associated with mental HRQoL subscales in PAPS thrombosis and executive functioning and memory were significantly associated with physical HRQoL subscales in PAPS pregnancy.

**Conclusions:** Cognitive impairment is associated with and is more prevalent in PAPS thrombosis patients when compared with PAPS pregnancy patients. Both PAPS groups demonstrate poor HRQoL which is associated with executive functioning and memory.

## Introduction

*Overview of APS*

Antiphospholipid syndrome (APS) is an autoimmune disease and is a prothrombotic condition defined by the presence of clinical event/s including venous/arterial thrombosis and/or pregnancy complications (pre-eclampsia, placental abruption, intra-uterine growth restriction) in association with laboratory blood tests confirming moderate-to-high titer antiphospholipid (aPL) antibodies and/or the presence of the lupus anticoagulant (Miyakis et al., 2006). APS may be primary (primary APS; PAPS) occurring as an isolated diagnosis, or it may be associated with other underlying autoimmune disorders. There is a high prevalence of APS among patients with Systemic lupus erythematosus (SLE) – also referred to as SLE-related APS (Tektonidou, Varsou, Kotoulas, Antoniou, & Moutsopoulos, 2006).

The clinical spectrum of APS features is extensive (D'Cruz, 2006) and central nervous system (CNS) involvement is one of the most common features including major neuropsychiatric manifestations such as stroke, seizures, migraine, transient ischaemic attack, chorea, psychosis, multiple-sclerosis (MS) like features, sensorineural hearing loss and mood disorders. Cognitive dysfunction is also a feature however it remains poorly recognised and relatively unexplored (Gordon, Goldenberg, Erkan & Lockshin, 2009; Pattanaik & Brey, 2006).

Where APS is characterised by the presence of moderate-to-high aPL antibodies, they can be present at low levels with an absence of clinical events and therefore asymptomatic patients testing positive for aPL antibodies do exist. However, these patients can experience some of the neuropsychiatric syndromes that those with definite APS experience such as seizures, chorea, migraine and cognitive dysfunction (Erkan, Kozora & Lockshin, 2011).

*Cognitive dysfunction in APS: Overview*

Cognitive deficits associated with APS can vary from mild neurocognitive disorders to severe global dysfunction in the context of dementia. Although interest in this area has increased in recent years, research is limited and few formal neuropsychological studies have been conducted to assess the prevalence and nature of cognitive deficits in patients with APS (Pattanaik & Brey, 2006). Studies evaluating neurocognitive deficits have mainly included SLE patients testing positive for aPL antibodies. Research distinguishing secondary APS and PAPS patients specifically is more limited and mainly anecdotal (Pattanaik & Brey, 2006). Findings so far have not identified any consistent pattern of cognitive dysfunction.

*Cognitive dysfunction, antiphospholipid (aPL) antibodies and Systemic lupus erythematosus*

Studies of SLE patients with aPL antibodies have shown that the antibodies may play a primary role in the pathogenesis of cognitive impairment and that the application of neuropsychological assessments has a use in detecting early neuropsychiatric involvement in these patients. Maeshima, Yamada, Yukawa and Nomoto (1992) reported that 72% of SLE patients (n = 21) with aPL antibodies demonstrated abnormal neuropsychological findings in visuoconstructive skills and verbal learning. Denburg, Carbotte, Ginsburg and Denburg (1997) revealed a significant association between SLE patients testing positive for aPL antibodies and cognitive impairment. These patients scored significantly lower than healthy controls (effect size range = .52 to 1.24) on most measures and SLE patients that tested negative for aPL antibodies (effect size range = .42 to .79) on measures of verbal memory, cognitive flexibility and psychomotor speed. Subsequent analysis of subjects from this study that did not have CNS involvement produced similar results. Leritz et al. (2002) found that aPL positive patients without CNS involvement (n = 29) performed significantly worse than aPL negative patients without CNS involvement (n = 27) on measures of neuropsychological

functioning including attention, concentration, visual search, spatial learning and memory. No clear pattern of cognitive impairment emerged. When the influence of depression was removed statistically, the aPL positive group still performed worse.

*Cognitive dysfunction in Primary APS and SLE-related APS*

Among studies that have included patients with a diagnosis of definite APS, most have focused on dementia or cognitive decline in an aging population (Gomez-Puerta et al., 2005). In studies which have explored the presence of less severe cognitive dysfunction, sample sizes have been small. Aharon-Peretz et al. (1995) investigated 20 patients with PAPS (14 with CNS involvement) and 10 healthy controls. Thirteen of the 14 patients with CNS disease had mild cognitive deficits across a number domains including; attention, semantic fluency, memory (working and visuospatial) and executive function (visuomotor and mental flexibility). Aharon-Peretz et al. (1995) did not include measures of emotional and or psychological distress. Mikdashi and Kay (1996) described 4 PAPS patients (without CNS involvement) with impairment in visual attention, executive function abilities and impairment in verbal and non verbal-memory skills.

Tektonidou et al. (2006) examined patients with PAPS (n = 39), SLE-related APS (n = 21), healthy controls (n = 60) and disease controls (n = 25). Forty two percent of the 60 patients with PAPS and SLE-related APS (combined) had cognitive deficits compared with 18% of healthy controls ($p = .005$). Deficits were common in verbal fluency, attention and scanning and visuomotor functions. Significant differences were found between all APS patients and all controls.

*Cognitive dysfunction and HRQoL*

As an autoimmune disease, APS is a chronic illness and patients live with the condition without a prospect of cure (de Ridder, 2004). The range of clinical features of APS, including cognitive dysfunction, are likely to impact upon aspects of patients' quality of life, where they may be presented with changes in their life roles and social and familial relationships while they concurrently manage psychological distress, physical pain, ongoing medical treatment and restrictions in the activities of daily living (Charmaz, 1983; Livneh & Antonak, 1997). Studies assessing patients' processes of adjusting to these changes have been informed by models of stress and coping which propose a complex and individual process with many physical, psychological, social and somatic factors (Lazarus & Folkman; 1984; Livneh & Antonak, 1997; Moos & Holahan, 2007). Research in patients with neurological conditions has utilised measures of Health Related Quality of Life (HRQoL) to tap into these broad dimensions as a way of measuring the influence of cognitive dysfunction on quality of life. Associations between cognitive impairment and poor HRQoL has been found in stroke patients (Hochstenbach, Anderson, Van Limbeck, & Mulder, 2001), patients with MS, (Amato, Ponziani, Siracusa, & Sorbi, 2001; Cutajar et al., 2000), brain tumours (Klein et al., 2003) and traumatic brain injury (Mitchell et al., 2010).

*Cognitive dysfunction and HRQoL in PAPS*

Research exploring the relationship between cognitive dysfunction in PAPS and the experience of illness and adjustment using HRQoL measures could not be found at the time of this study. As research with SLE patients highlights significant factors for PAPS patients it is useful to consider findings of research exploring HRQoL in this clinical population. Studies indicate that scores on HRQoL measures have been 30 - 40% lower than those reported by matched peers (Sweet, Doninger, Zee, & Wagner, 2004) with all domains of HRQoL affected

by SLE (Fortin, et al., 1998; Wang, Mayo, & Fortin, 2001). Studies exploring cognitive dysfunction in relation to HRQoL in SLE are scarce. The most recent is that of Tam et al. (2008) which investigated the association of neuropsychiatric manifestations, including cognitive functioning, depression and anxiety and HRQoL in 291 Chinese SLE patients. Findings demonstrated that cognitive impairments of executive functioning were associated with impairment on the mental health subscale of a HRQoL measure.

Where occupational status is one objective measure of global functioning that correlates with QoL ratings in a variety of medical disorders, there are studies that have explored this specifically (Panopalis et al., 2007; Utset, Fink, & Doninger, 2006). Utset et al. (2006) demonstrated the influence of cognitive impairment on work status in 50 SLE patients. Fifty percent of patients had cognitive impairment; the 16% that had self report work disability were more likely to have neurocognitive dysfunction and poor quality of life. Panopalis et al. (2007) assessed the contribution of memory impairment to employment status in 832 patients with SLE. Those with mild-moderately or severely impaired verbal memory experienced greater work disability than those with intact memory function. Even mild memory impairment interfered with work as key aspect of quality of life.

*Summary*

Primary APS is a chronic illness with many clinical features including cognitive dysfunction ranging from mild to severe. However, cognitive dysfunction remains poorly recognised (Gordon, et al., 2009). As the population that most closely resembles PAPS includes SLE patients testing positive for aPL antibodies, it is research in this population that contributes to knowledge and can inform research in PAPS. Of the few studies with this population and APS patients, findings demonstrate cognitive deficits in groups with and without overt CNS involvement in a variety of domains. However, there appears to be no

specific pattern of cognitive impairment nor is there clarity about the role of physical, psychological, social and somatic experiences and their association with cognitive deficits in these clinical groups.

It is expected that the number of patients with APS and the number recognised as having APS will grow (Kasthuri & Roubey, 2009). Therefore a better understanding of the nature of cognitive dysfunction in PAPS and the influence it has on quality of life is theoretically and clinically important in informing the development of treatment approaches. This study aims to address this, utilising sensitive well validated and reliable HRQoL and neuropsychological measures to examine the relationship between cognitive functioning and quality of life in patients with PAPS. Further aims of this study are to establish the characteristics and prevalence of cognitive dysfunction and HRQoL in PAPS. It is hypothesised that PAPS patients will demonstrate i) impaired cognitive functioning on all neuropsychological measures and ii) impaired HRQoL in all domains of the HRQoL measure and that iii) cognitive functioning will be positively correlated with HRQoL.

## Method

*Study design and participants*

In this cross-sectional study, performance on measures of cognitive function and HRQoL were compared in patients with PAPS and healthy controls. Participants included 30 female patients with definite PAPS - diagnosed according to the Sydney Criteria (Miyakis et al., 2006). Patients were divided between those who had experienced vascular thrombosis (n = 15; PAPS thrombosis) and those who had experienced pregnancy complications (n = 15; PAPS pregnancy). Patients were recruited from a large London medical centre between September 2010 and May 2011. The control group (n = 15) consisted of a convenience

sample of healthy volunteers personally known to the researcher and research assistants. The volunteers were recruited from the London, the South West and South East of the United Kingdom.

*Exclusion criteria*

As PAPS defined by pregnancy complications includes females only, and in order for the groups to be as closely matched as possible, the vascular thrombosis and healthy control groups excluded males. To ensure any cognitive and psychosocial problems identified in this study relate to PAPS it was important to exclude individuals with a medical or psychiatric history and/or major neuropsychiatric manifestations (stroke, transient ischemic attacks, chorea and demyelinating disorders) that might otherwise account for their symptoms. Participants were excluded if they were pregnant or lactating; had experienced a very recent ($\leq$ 3 months) thrombotic event or pregnancy loss; had a diagnosis of SLE, any other definite autoimmune connective tissue disorder (one participant had Rheumatoid Arthritis), fibromyalgia, chronic fatigue syndrome or chronic viral infections (such as HIV, Hepatitis B or C); were using anti-psychotic or anti-depressant medication or had a known history of drug misuse. Individuals who were non-English speaking were also excluded due to the nature of measures utilised in this study.

*Power analysis*

Power calculations were made using the Gpower software package (Erdfelder, Faul & Buchner, 1996). For significant univariate analysis of variance (ANOVA) at a 0.05 level of significance, a power of 0.80 and a medium effect size (Cohen, 1969; $d = 0.5$), 42 participants in total are required. For significant Pearson's product-moment correlations at a .05 level of

significance, a power of 0.80 and medium effect size (Cohen, 1969; $r = 0.4$), 37 participants in total are required.

*Procedure*

Potential participants were identified by consultants and a research nurse when they attended their hospital clinic appointment. They were provided with written and verbal information about the study. If they agreed to take part, their contact details were given to the researcher so that an appointment could be made at a mutually convenient time to complete the measures.

Participants in the clinical groups met with the researcher or a research worker (assistant psychologists) at the hospital for 2.5 hours to complete a battery of neuropsychological assessments and questionnaires measuring HRQoL and mood. Those administering the assessments were not aware of the participant's medical status and were therefore blind to which group they were in. Two participants could not attend the hospital to participate (one due to anxiety relating to travelling by public transport and one due to difficulties with childcare arrangements) - they were visited in their homes to undergo the assessments. Participants in the healthy control group were visited at their home or at their place of work to complete the assessments.

*Ethical approval*

Ethical approval for this study was granted by the National Health Service (NHS) Research Ethics Committee (Appendix B) and NHS Research and Development for the participating trust (Appendix C). All participants were informed about the nature and purpose of the study and of the way data would be handled. This information was provided by the

research nurse, the researchers and on an information sheet (Appendix F). Written informed consent was obtained by all those who took part.

*Measures of neuropsychological function*

A psychometric battery of tests to cover a range of cognitive functions was administered comprising measures that are routinely used in clinical practice within the NHS. All tests have adequate published reliability, validity and normative data and included:

The *Wechsler Abbreviated Scale of Intelligence* (WASI; Wechsler, 1999; Appendix S) is an abbreviated version of the full battery of intellectual functioning measure, the Wechsler Adult Intelligence Scale III (WAIS III; Wechsler, 1998). It is standardised on the U.S population and comprises four subtests that measure verbal, non-verbal and general cognitive functions. Raw scores for each subtest are converted to standardised scores. The Vocabulary subtest, which assesses expressive vocabulary and verbal knowledge and the Similarities subtest, which measures verbal concept formation and abstract reasoning ability, form the Verbal Scale and yield a Verbal IQ score (VIQ). The Block design subtest, which assesses spatial visualisations, visual motor coordination and abstract conceptualisation and the Matrix Reasoning subtest, which assesses nonverbal fluid reasoning and general intellectual ability, form the Performance Scale and yield the Performance IQ (PIQ). The four subtests comprise the full scale and yield the Full Scale Intellectual Quotient (IQ; FSIQ). Reliability coefficients represent a high level of internal consistency with ranges as follows: Vocabulary, 0.90 to 0.98; Similarities, 0.84 to 0.96; Block Design, 0.90 to 0.94; Matrix Reasoning, 0.88 to 0.96. The reliability coefficients for the scale scores ranged from 0.92 to 0.98 for VIQ and 0.94 to 0.97 for PIQ. The reliability coefficients for Full Scale IQ scores ranged from 0.96 to 0.98 for the full FSIQ-4 (Garland, 2005). The similarity between the items in the WASI and the parallel items in the WAIS III ensure that the content validity is maintained (Garland, 2005).

*Wechsler Adult Intelligence Scale III* (WAIS III $^{UK}$; Wechsler, 1998)

The WAIS III$^{UK}$ is a full battery of psychometric intelligence assessments also standardised on the US population but with small modifications to create a UK version (Wechsler, 1998). It contains fourteen subtests each measuring different facets of intelligence. The subtests include four subtests of the WASI (see above) as well as Information, Picture Completion, Arithmetic, Digit Span, Letter-Number Sequencing, Digit Symbol Coding and Symbol Search. Raw scores for each test are converted to standardised scores. The WAIS III also yields the three composite scores; VIQ, PIQ and FSIQ. Three subtests were used from the WAIS III$^{UK}$ including: Digit Span, to measure information processing and complex attention, Digit Symbol Coding, to measure visual motor co-ordination and processing speed and Symbol Search, to measure visual perception and motor speed (Appendix T). Average reliability coefficients for these subtests were .90, .84 and .77 respectively. The subtests for the WAIS III are reported to have good content and construct validity (Silva, 2008).

*The National Adult Reading Test* (NART; Nelson, 1982) is a test with good reliability (reliability coefficient 0.93) and validity (Crawford, Dreary, Starr & Whalley, 2001) commonly used to estimate pre-morbid intellectual functioning (Appendix U). It is a 50 single item word reading test of graded difficulty. The examinee reads each word aloud and the number of errors made is recorded. WAIS VIQs, PIQs and FSIQs can be predicted from the reading error score. The NART was standardised on a series of 120 patients between the ages of 20 and 70 with extra-cerebral disorders, mainly spinal cord disorders and neuropathies. Research indicates that NART performance is not greatly influenced by the effects of many neurological and psychiatric disorders, as judged by the absence of significant differences between the clinical and control samples.

*Delis Kaplan Executive Function System* (DKEFS, Delis, Kaplan, & Kramer, 2001) is a set of standardised tests consisting of nine subtests that measure a wide spectrum of verbal

and non-verbal executive functions. The tests include: Trail Making Test, Verbal Fluency Test, Design Fluency Test, Colour-Word Inference Test, Scoring Test, Twenty Questions Test, Word Context Test, Tower Test and Proverb Test. Each test is designed to be used either as a stand alone test or along with other DKEFs tests. Raw scores for each test are converted to standardised scores. The DKEFS standardisation sample consisted of 1,750 children, adolescents and adults aged 8 to 89 years (Delis, Kaplan, & Kramer, 2001), selected to match the demographic characteristics of the US population.

Two subtests were administered; the Verbal Fluency Test (reliability coefficient range 0.53 to 0.65) which consists of three conditions and assesses the ability to generate words fluently in an effortful, phonemic format (letter fluency test), from overlearned concepts (category fluency test) and simultaneously shifting between overlearned concepts (category switching test) (Appendix V). The test uses the number of words given in each task within a time period of 60 seconds to generate a scaled score. The Trail Making Test (reliability coefficient range 0.20 to 0.82) which measures cognitive flexibility on a visual motor task (Appendix W) was also administered. This test consists of five conditions which assess visual scanning, number sequencing, letter sequencing, letter-number switching and motor speed. The primary executive function measured by the test is cognitive flexibility in the fourth condition (letter-number switching; Delis et al., 2001). Conditions one, two, three and five provide baseline information about component skills to factor out their influence in the executive function domain assessed in condition four. This test uses time to complete each task to generate a scaled score (Delis et al., 2001).

*The Brain Injury and Rehabilitation Trust (BIRT) Memory and Information Processing Battery* (BMIPB) (Coughlan, Oddy, & Crawford, 2007) assesses memory and information processing skills. There are four versions (Forms 1, 2, 3 and 4) allowing for assessments to be repeated without the problem of content specific practice effects. The test

comprises three verbal memory tasks (Story Recall, List Learning and List Recognition), three visual memory tasks (Figure Recall, Design Learning and Design Recognition) and an information processing task (Number Cancellation). Two of the tests were administered, Story Recall (Form 1; Appendix Y) and Figure Recall (Form 1; Appendix Z). In the Story Recall task, examinees are read a story and asked to recall it immediately and then again 40 minutes later. For Figure Recall, examinees copy a complex 2D figure and then are asked to reproduce it from memory immediately and then 40 minutes later. Scores for the tests are norm based, calculated by a BMIPB computer program providing regression based norms using age and education level as predictors. Normative data for the BMIPB were obtained from 300 participants within the UK population within the age range 16-89. The sample recruited was intended to reflect as closely as possible the distribution of age, educational level and gender within the general population.

*Camden Memory Tests* (CMT; Warrington, 1996) include a standardised battery of five tests of different aspects of memory and learning. The tests include the Pictorial Memory Test, the Topographical Recognition Memory Test, the Paired Associate Learning Test, the Short Recognition Memory Test for Words (CSRMT-W) and the Short Recognition Memory Test for Faces (CSRMT-F). Both the CSRMT-W and CSRMT-F (Appendix Z1) are visual memory tests and were administered in this study to assess material specific memory deficits. The tests require forced-choice recognition of faces and words. The stimuli consist of 25 stimulus words and faces. In the recognition test, words/faces are paired with 25 distractor words/faces. The tests were standardised on adults aged 18-85 educated in the school system. Raw scores can be converted to percentile scores for three age groups 18-49, 50-69 and 70-85. Percentile scores were converted to scaled scores for this study.

*The Graded Naming Test* (GNT; McKenna & Warrington, 1983) is a validated verbal fluency test measure which assesses object-naming ability (McKenna & Warrington, 1983;

Appendix Z2). The test involves the oral naming of 30 pictures of objects, scoring reflects this and so raw scores range from 0 to 30. The 100 people of 'average' intelligence in the standardisation sample with an age range of 18 to 77 had a mean score of 20.4 (SD = 4.1) (Lezak, 2004). Raw scores can be converted to scaled scores based on those of the WAIS vocabulary subtest; this converts to a scaled score of 11. The GNT is graded in difficulty to allow for individual differences and is therefore able to detect word-finding difficulty even in those with an extensive naming vocabulary. The GNT demonstrates good reliability and (0.92) has been found to be sensitive to even small cognitive changes (Bird, Papadopoulou, Ricciardelli, Rossor, & Cipolotti, 2004).

*Measure of HRQoL*

The *Medical Outcomes Survey Short Form-36* (SF-36; Ware & Sherbourne, 1992) was used to measure HRQoL (Appendix Z3). This is a 36-item inventory (Stewart, Hays & Ware, 1988) and is a widely used generic measure of HRQoL across a variety of clinical populations. The measure generates 8 subscales: 1) physical functioning, 2) role limitations due to physical problems, 3) bodily pain, 4) general health perceptions, 5) vitality, 6) social functioning, 7) role limitations due to emotional problems and 8) mental health. These scales, weighted according to normative data are scored from 0 – 100 and are T scores (mean = 45 standard deviation = 10). For group level data T scores of 47 are considered 'average'. Scores higher than 47 therefore reflect better HRQOL and T scores less than 47 indicate impaired functioning or well-being. Algorithms were developed by the originators of the SF-36 to calculate 2 psychometrically based summary scores: the physical component summary (PCS; subscales 1-4 above) and mental health component summary (MCS; subscales 5-8 above) (internal consistency reliability estimates of 0.95 and 0.93 respectively; Ware et al., 2007). The PCS and MCS provide greater precision, reduce the need for statistical comparisons

needed and eliminate the floor and ceiling effects in several of the subscales (Ruta, Hurst, Kind, Hunter, & Stubbings, 1998). There is evidence for reliability and validity of the SF-36 in SLE populations (Panapalis & Clark, 2006).

*Measure to screen for depression*

The *Hospital Anxiety and Depression Scale* (HADS; Zigmond & Snaith, 1983) (Appendix Z4) was designed to measure mood disorders in populations with physical illness. It consists of 14 items which are scored between 0 and 3 and summed to provide two scores: one for anxiety and one for depression. Scores of 11 or higher indicate probable depression and are divided into four ranges: normal (0-7) mild (8-10), moderate (11-15) and severe (16-21). For the purposes of this study, the HADS was used as a screening tool to assess depression. The HADS has demonstrated good validity and reliability and has been widely used in research (Bjelland, Dahl, Haug, & Neckelmann, 2002).

*Administration of measures and management of data*

All measures were administered by either the researcher or research workers who were all experienced in administering these assessments. Further training was also completed prior to the research commencing to ensure tests would be administered consistently. The order in which assessments were administered was as follows: HADS, SF-36, NART, BIRT Story and Figure - Immediate Recall, WASI, BIRT Story and Figure - Delayed Recall, WAIS subtests (digit symbol coding, digit span, symbol search), Camden Memory Battery subtests (visual and verbal), Graded Naming Test. The researcher assessed twenty-two of the forty-five participants. All data were scored and subsequently managed by the researcher.

*Data analysis*

To have a direct comparison between tests, raw scores from the neuropsychological tests were transformed into scaled scores. All variables were assessed for assumptions of normality and homogeneity of variance using the Kolmogorov-Smirnov test and Levene's test respectively. Some data significantly violated these assumptions. In group comparisons of neuropsychological outcomes and HRQoL, one-way ANOVA and Bonferroni's post hoc tests and Kruskal-Wallis and Mann-Whitney U non-parametric tests were used as appropriate. Because of the multiple comparisons, the Bonferroni significance threshold was set at p = 0.025 for post hoc comparisons. Results were expressed as mean (*M*) and standard deviation (*SD*) for normally distributed data. Data that violated assumptions was expressed as median (*mdn*) and range. Wilcoxon signed-ranks test was used to compare pre-morbid and current levels of intellectual ability in PAPS patients. A criterion for cognitive impairment was a score in the pathologic range (i.e. performance below the $5^{th}$ centile of the normal population) in two or more tests (Monastero et al., 2001). The number of patients fulfilling this criterion in each group was compared by means of a contingency table (chi-square statistics).

Spearman's rho and Pearson's correlation coefficient were used to examine correlations between neuropsychological outcomes and HRQoL scores. The possible effect on HRQoL was assessed further by multiple regression analysis (forced entry) where there were two or more significant positive correlations between neuropsychological measures and HRQoL scores. Comparisons between the three groups, Controls, PAPS pregnancy and PAPS thrombosis, for demographic and clinical characteristics were performed using descriptive statistics, parametric tests (one-way ANOVA) and non-parametric tests (Kruskal-Wallis). Analyses were performed using SPSS for Windows, version 17.0.

## Results

*Demographic and clinical characteristics*

Demographic and clinical characteristics appear in Table 1. Thirty female patients and 15 healthy controls were recruited; there were no significant differences in age, education and pre-morbid IQ. The median scores for depression on the HADS fell within the 'normal' range indicating that participants were not depressed. There was, however, a significant difference between scores $H(2) = 7.08$, $p<.05$.

**Table 1** Demographic and clinical characteristics of PAPS patients and healthy controls

| | Control (n=15) Median (range) | PAPS Pregnancy (n=15) Median (range) | PAPS Thrombosis (n=15) Median (range) |
|---|---|---|---|
| Age | 49.00 (23-57) | 40.00 (29-47) | 46.00 (30-50) |
| Years of Education | 17.00 (11-19) | 17.00 (14-19) | 14.00 (12.00-19.00) |
| Pre-morbid IQ (NART) | 118 (100-125) | 114 (100-125) | 119 (89-122) |
| HADS Depression Score* | 1.00 (0-12) | 4.00 (1-12) | 5.00 (1-15) |

*<.05

*Neuropsychological assessment*

Intergroup comparisons indicate that patients with PAPS thrombosis and PAPS pregnancy demonstrated lower scores than control subjects (Table 2). Kruskal Wallis tests revealed significant differences for four neuropsychological outcomes: WAIS Symbol Search, $H(2) = 7.50$, $p < .05$, Trail Making 1, $H(2) = 6.41$, $p < .05$, Trail Making 5 $H(2) = 6.97$, $p < .05$ and CSRMT-F, $H(2) = 11.09$, $p < .01$. Mann Whitney tests were used to follow up this finding. A Bonferroni correction was applied so all effects are reported at a .025 level of significance. Effect sizes (*r)* for significant findings ranged from 0.42 to 0.54. PAPS thrombosis patients performed at a significantly lower level than controls on each of the four tests: WAIS Symbol Search ($U = 57.5$, $r = -.42$); Trail Making 1 ($U = 56.5$, $r = -.43$), Trail Making 5 ($U = 56.0$, $r = -.43$) and CSRMT-F ($U = -.54$, $r = -.54$). There were no significant

differences between PAPS pregnancy patients and controls on these neuropsychological outcomes.

Comparisons between estimated pre-morbid IQ (NART) and current IQ (WASI FSIQ) were made using Wilcoxon signed-rank test. There had been a significant reduction between PAPS thrombosis group's estimated pre -morbid IQ (*mdn* = 119) and their current level of general intellectual ability (*mdn* = 109), $Z$= -2.29, $p < .05$, $r$ = 0.6. Based on the decline between estimated pre-morbid IQ and current IQ, intellectual ability appeared to have reduced in PAPS pregnancy patients; the change was not significant.

**Table 2** Analysis of Variance (ANOVA) and non-parametric tests comparing Controls and PAPS groups on neuropsychological outcomes

| **Cognitive Domain/** Neuropsychological outcomes | Control (n=15) Mean (SD) / Median (Range) | PAPS Pregnancy (n=15) Mean (SD) / Median (Range) | PAPS Thrombosis (n=15) Mean (SD) / Median (Range) | Test | F value/ H value |
|---|---|---|---|---|---|
| **General Intelligence** | | | | | |
| WASI Vocabulary | 11.93 (3.32) | 11.20 (2.90) | 11.53 (3.70) | A | 0.18 |
| WASI Similarities | 11.53 (2.41) | 11.40 (2.19) | 11.13 (2.41) | A | 0.11 |
| WASI Block Design | 11.40 (2.09) | 12.00 (2.36) | 10.60 (2.99) | A | 1.17 |
| WASI Matrix Reasoning | 12.93 (1.98) | 12.40 (2.02) | 12.20 (1.89) | A | 0.56 |
| WASI Verbal IQ | 109.13 (14.4) | 106.47 (12.3) | 107.07 (15.00) | A | 0.15 |
| WASI Performance IQ | 111.87 (10.87) | 111.73 (10.30) | 108.07 (12.45) | A | 0.55 |
| WASI Full-scale IQ | 111.73 (12.59) | 110.13 (9.1) | 108.33 (10.49) | A | 0.37 |
| **Executive Functioning** | | | | | |
| WAIS Digit Symbol Coding | 10.60 (2.53) | 10.00 (1.41) | 8.67 (2.99) | A | 2.54 |
| WAIS Digit Span | 11.60 (2.38) | 10.40 (2.61) | 11.07 (3.17) | A | 0.72 |
| WAIS Symbol Search | 12.00 (9-18) | 12.00 (9-15) | 10.00 (4-15) | K-W | 7.50* |
| DKEFS Letter Fluency | 12.13 (3.46) | 11.53 (2.69) | 11.00 (4.01) | A | 0.41 |
| DKEFS Category Fluency | 13.07 (3.30) | 12.07 (3.61) | 11.40 (2.94) | A | 0.97 |
| DKEFS Category Switching Responses | 12.93 (3.90) | 11.13 (2.87) | 11.27 (4.52) | A | 1.03 |
| DKEFS Category Switching Accuracy | 12.13 (4.82) | 11.53 (2.41) | 11.73 (3.97) | A | 0.09 |
| DKEFS Trail Making 1 | 11.00 (8-13) | 10.00 (5-13) | 10.00 (1-12) | K-W | 6.41* |
| DKEFS Trail Making 2 | 11.00 (8-13) | 10.00 (4-12) | 8.00 (1-15) | K-W | 5.86 |
| DKEFS Trail Making 3 | 12.00 (6-15) | 11.00 (6-12) | 10.00 (11-15) | K-W | 4.95 |
| DKEFS Trail Making 4 | 11.00 (6-16) | 10.00 (1-12) | 10.00 (1-13) | K-W | 4.48 |
| DKEFS Trail Making 5 | 10.00 (5-12) | 10.00 (7-13) | 7.00 (2-12) | K-W | 6.97* |
| DKEFS Trail Making Composite Score | 12.00 (7-16) | 12.00 (15-18) | 10.00 (5-16) | K-W | 5.73 |
| **Memory** | | | | | |
| Camden Memory Test Faces | 12.80 (10-13) | 13.00 (8-13) | 12.00 (6-13) | K-W | 11.09** |
| Camden Memory Test Words | 13.00 (10-13) | 13.00 (8-13) | 13.00 (1-13) | K-W | 1.65 |
| BIRT Story Recall Immediate | 8.47 (3.58) | 8.20 (3.23) | 8.33 (2.79) | A | 0.26 |
| BIRT Story Recall Delayed | 9.53 (3.39) | 8.93 (3.30) | 9.27 (2.65) | A | 0.14 |
| BIRT Figure Recall Immediate | 9.74 (4.48) | 9.64 (2.79) | 8.20 (3.38) | A | 0.841 |
| BIRT Figure Recall Delayed | 9.00 (3.02) | 10.21 (2.25) | 8.80 (2.21) | A | 1.32 |
| Graded Naming | 13.00 (9-15) | 12.00 (9-15) | 13.00 (7-15) | K-W | 0.81 |

*** <.000; ** < .01; * <.05
A = ANOVA, K-W = Kruskal-Wallis

Data of prevalence of cognitive impairment between the PAPS groups can be seen in Table 3. PAPS thrombosis patients demonstrated greater impairment in domains of general intelligence; both groups demonstrated impairment in domains of executive functioning and memory. Twenty percent of patients in both groups showed impairment on the primary

measure of executive functioning (Trail Making 4) and verbal logical memory (BIRT Story Recall Immediate). Furthermore, 26.7% of PAPS pregnancy patients were impaired on a measure of delayed memory (BIRT Story Recall Delayed). The PAPS thrombosis group (6.7%) also showed poor functioning in 3 of the 4 WASI IQ subtests (verbal subtests and one performance subtest). Cognitive impairment was identified in four out of 15 (26.7%) in PAPS pregnancy patients and eight out of 15 (53.3%) in PAPS thrombosis patients as measured by abnormal performance in two or more tests (*p* = .264, two tailed Fisher's exact test).

**Table 3** Prevalence of cognitive impairment in PAPS Pregnancy and PAPS Thrombosis subjects[a]

| **Cognitive Domain/** Neuropsychological outcomes | PAPS Pregnancy (n=15) *n ( %)* | PAPS Thrombosis (n=15) *n ( %)* | p [b] |
|---|---|---|---|
| **General Intelligence** | | | |
| WASI Vocabulary | - | 1(6.7) | ns |
| WASI Similarities | - | 1 (6.7) | ns |
| WASI Block Design | - | 1 (6.7) | ns |
| WASI Matrix Reasoning | - | - | - |
| **Executive Functioning** | | | |
| WAIS Digit Symbol Coding | - | 2 (13.3) | ns |
| WAIS Digit Span | - | - | - |
| WAIS Symbol Search | - | 1 (6.7) | ns |
| DKEFS Letter Fluency | - | - | - |
| DKEFS Category Fluency | 1 (6.7) | 1 (6.7) | ns |
| DKEFS Category Switching Responses | - | 1 (6.7) | ns |
| DKEFS Category Switching Accuracy | - | 1 (6.7) | ns |
| DKEFS Trail Making 1 | 1 (6.7) | 2 (13.3) | ns |
| DKEFS Trail Making 2 | - | 3 (20) | ns |
| DKEFS Trail Making 3 | - | 1 (6.7) | ns |
| DKEFS Trail Making 4 | 3 (20) | 3 (20) | ns |
| DKEFS Trail Making 5 | - | 2 (13.3) | ns |
| **Memory** | | | |
| Camden Memory Test Faces | - | - | ns |
| Camden Memory Test Words | - | 1 (6.7) | ns |
| BIRT Story Recall Immediate | 3 (20) | 3 (20) | ns |
| BIRT Story Recall Delayed | 4 (26.7) | 1 (6.7) | ns |
| BIRT Figure Recall Immediate * | 1 (7.1) | 3 (20) | ns |
| BIRT Figure Recall Delayed * | - | 1 (6.7) | ns |
| Graded Naming | - | - | |

* n=14 in both groups
[a] Number/percentage of patients impaired [b] Not Significant after Fisher's Exact test)

*HRQoL*

The scores for HRQoL, including all eight subscales and the PCS and MCS scores were significantly lower in PAPS thrombosis patients and PAPS pregnancy patients compared with controls (Table 4). The PAPS pregnancy patients had a lower Bodily Pain score (*Mdn* = 50) compared with both PAPS thrombosis (*Mdn* = 51.13) and controls (*Mdn* = 62.12). Median scores were below 47 on six of the SF-36 subscales and the PCS and MCS for PAPS thrombosis patients and median scores on five subscales and the MCS were below 47 for PAPS pregnancy patients indicating impaired quality of life.

**Table 4** Analysis of Variance (ANOVA) and non-parametric tests comparing Controls and PAPS groups on SF-36 subscales

| SF-36 Subscales | Control (n=15) Mean (SD) / Median (Range) | PAPS Pregnancy (n=15) Mean (SD) / Median (Range) | PAPS Thrombosis (n=15) Mean (SD) / Median (Range) | Test | F value/ H value |
|---|---|---|---|---|---|
| SF-36 Physical Functioning | 57.03 (47-57) | 52.82 (15-57) | 42.30[a] (21-57) | K-W | 9.16** |
| SF-36 Role Physical | 56.85 (37-57) | 49.51 (20-57) | 37.26[a] (18-57) | K-W | 19.92*** |
| SF-36 Bodily Pain | 62.12 (37-62) | 50.29 (20-62) | 51.13 (29-62) | K-W | 9.22** |
| SG-36 General Health | 55.32 (46-64) | 43.40[a] (19-55) | 28.15[a] (19-55) | K-W | 18.69*** |
| SF-36 Vitality | 53.54 (8.24) | 43.13[a] (11.18) | 40.22[a] (11.20) | A | 6.92** |
| SF-36 Social Functioning | 56.85 (30-57) | 40.49[a] (13-57) | 35.03[a] (24-57) | K-W | 9.94 |
| SF-36 Role Emotional | 51.99 (21-56) | 48.10 (33-56) | 48.10 (13-56) | K-W | 1.88 |
| SF-36 Mental Health | 48.69 (8.37) | 45.46[a] (8.88) | 44.56[a] (8.80) | A | 0.93 |
| SF-36 Physical Component Score | 58.38 (48-70) | 49.21 (7-60) | 44.09[a] (15-59) | K-W | 1.97 |
| SF-36 Mental Component Score | 51.20 (13-58) | 46.11[a] (28-60) | 41.34[a] (27-59) | K-W | 3.98 |

*** <.000; ** < .01; * <.05
A = ANOVA, K-W = Kruskal-Wallis
[a]Scores < 47 indicates impaired HRQoL

Kruskal-Wallis tests showed there was a significant difference on five HRQoL subscales including Physical Functioning, $H(2) = 9.17$ $p < .01$; Role Physical, $H(2) = 19.92$, $p < .000$; Bodily Pain, $H(2) = 9.22$, $p < .01$; General Health, $H(2) = 18.70$, $p < .000$ and Vitality, $F(2, 12) = 6.92$, $p < .01$, $\omega^2 = 1.9$ ($\omega^2$= omega squared effect size). Mann Whitney tests and Bonferroni's test were used to follow up these findings. A Bonferroni correction was

applied so effects are reported at a .025 level of significance (.05/2). Effect sizes (*r)* for significant findings ranged from 0.4 to 0.7. Mann Whitney post hoc tests demonstrated a significant difference between PAPS thrombosis patients and controls on Physical Functioning ($U$ = 50.5, $r$ = -.05), Role Physical ($U$ = 23.5, $r$ = -0.7), Bodily Pain ($U$ = 63.0, $r$ = -0.4), General Health ($U$ = 26.5, $r$ = 0.7). Bonferroni's test showed a significant difference ($p < .01$) between controls ($M$ = 53.54, $SD$ = 8.24) and PAPS thrombosis patients ($M$ = 40.22, $SD$ = 11.20) on the Vitality subscale. Significant differences between PAPS pregnancy patients and controls on these subscales were also found: Physical Functioning ($U$ = 54.00, $r$ = - 0.5), Role Physical ($U$ = 25.50, $r$ = 0.6), Bodily Pain ($U$ = 41.00, $r$ = 0.6), General Health ($U$ = 20.50, $r$ = 0.7). Bonferroni's test showed a significant difference between controls ($M$ = 53.54, $SD$ = 8.24) and PAPS pregnancy patients ($M$ = 43.13, $SD$ = 11.18) ($df$ = (2), $p \leq .025$) on the Vitality subscale.

*Neuropsychological assessment and HRQoL*

To investigate whether observed neuropsychological outcomes were associated with the eight SF-36 subscales and PCS and MCS scores, correlational analyses were carried out. To avoid bias and determine false discovery rate, all neuropsychological outcomes were entered into the analysis, not just those shown to be impaired on the group analysis (Tables 5A and 5B, Appendix R).

Pearson's and Spearman's correlations revealed that there were eight neuropsychological outcomes in all three cognitive domains that significantly correlated with HRQoL on all of the MCS subscales in the PAPS thrombosis patients group indicating an association between cognitive functioning and aspects of mental health. WASI Block Design, $r$ = .48, $p$ (one-tailed) < .05, Matrix Reasoning, $r$ = .52, $p$ (one-tailed) < .05, WASI Performance IQ, $r$ =.58, $p$ (one-tailed) < .05 and BIRT Figure Recall Delayed, $r$ = .45, $p$ (one-

tailed) < .05 were significantly related to Role Emotional; WAIS Digit Span was significantly correlated with Mental Health, $r$ = .50, $p$ (one -tailed) < .05; DKEFS Trail Making 2 was significantly related to Vitality, $r_s$ = .56, $p$ (one-tailed) < .05, and CSRMT-F was significantly related to Social Functioning, $r_s$ =.55 $r$ = .50, $p$ (one-tailed) < .05. Three subtests were significantly correlated with the MCS; Digit Span, $r$ = .59, $p$ (one -tailed) < .05, DKEFS Trail Making 1, $r$ = .51, $p$ (one-tailed) < .05 and CSRMT-F, $r_s$ = .47, $p$ (one-tailed) < .05. One neuropsychological outcome (DKEFS Trail Making 2) was significantly correlated with one PCS subscale, General Health, $r$ = .58, $p$ (one -tailed) < .05. CSRMT-F was also significantly related to the PCS, $r_s$ = .56, $p$ (one -tailed) < .05. These findings indicate some association between executive functioning and memory and aspects of physical health.

In PAPS pregnancy patients, there were five neuropsychological outcomes in two cognitive domains (executive functioning and memory) that significantly correlated with three PCS subscales: WASI Digit Symbol Coding, $r$ = .50, $p$ (one -tailed) < .05, DKEFS Trail Making 4, $r_s$ =.49, $p$ (one -tailed) < .05 and CSRMT-F, $r$ =. 59, $p$ (one -tailed) < .01 all significantly correlated with Role Physical, WAIS Digit Span, $r$ = .52, $p$ (one -tailed) < .05 was significantly related to General Health. There was a significant relationship between CSMT-W on the MCS $r_s$ = .45, $p$ (one-tailed) < .05 and 2 MCS subscales; Role Emotional $r_s$ = .60, $p$ (one -tailed) < .01 and Mental Health, $r_s$ = .48, $p$ (one -tailed) < .05. The DKEFS Trail Making 4 was also significantly correlated with Mental Health, $r_s$ = .57, $p$ (one-tailed) < .05

There were a further twenty neuropsychological outcomes in PAPS pregnancy patients which significantly correlated with HRQoL scores compared with six in the PAPS thrombosis group. These correlations were not in the expected direction and were not consistent with the hypothesis. Details can be seen in Tables 5A and 5B (Appendix R). Findings are only summarised in this text and will be addressed in the discussion. In PAPS pregnancy patients,

nine of the 20 significantly correlated neuropsychological variables in all 3 cognitive domains related to Physical Functioning, Role Physical, Bodily Pain, Vitality, Role Emotional and the PCS. Eleven outcomes within the domains of memory and executive functioning were significantly related to Role Physical, General Health, Mental Health and PCS. In PAPS thrombosis patients, neuropsychological outcomes within memory and executive functioning were significantly correlated with Bodily Pain, General Health, Vitality, Social Functioning and Role Emotional.

To evaluate the extent to which neuropsychological outcomes predict domains of HRQoL multiple regression analyses were calculated where two or more neuropsychological outcomes significantly positively correlated with SF-36 subscales scores and the MCS and PCS. SF-36 domains were entered as dependent variables. For Role Physical in PAPS pregnancy patients, the CSRMT-F and WAIS Digit Symbol Coding were all highly correlated when put into a regression model and became non-significant. This was also true for Role Emotional and WASI Performance IQ and BIRT Figure Recall Delayed and for the MCS and WASI performance IQ, DKEFS Trail Making 1 and CSRMT-F in PAPS thrombosis patients,. However these findings strengthen those of the correlation analysis.

## Discussion

The aims of this study were to establish the characteristics and prevalence of neuropsychological deficits and impairments in HRQoL in patients with PAPS. A further aim was to identify relationships between cognitive functioning and HRQoL. As far as it is known, this is the first study to investigate these variables in this clinical population.

In comparing neuropsychological outcomes in terms of estimated pre-morbid IQ, as assessed by the NART, and obtained current IQ, as measured by the WASI, PAPS thrombosis

patients appeared to demonstrate a significant deterioration in their general intellectual abilities**.** Further comparisons on individual cognitive variables demonstrated significantly poorer functioning in the PAPS thrombosis group compared with controls on measures of visual memory (CSRMT-F) and executive functioning (WASI Symbol Search; DKEFS Trail Making 1 and 5). PAPS pregnancy patients also performed more poorly on these measures compared to controls though not significantly. These findings are consistent with previous research in patients with PAPS (Aharon-Peretz et al., 1995; Mikadashi & Kay, 1996) and SLE patients with aPL antibodies (Denburg et al., 1997). Together these results suggest a pattern of neuropsychological deficits associated with PAPS and aPL antibodies relating to memory and more convincingly, executive functioning.

The findings indicate that cognitive impairment occurred more frequently in PAPS thrombosis patients (n=8) compared to PAPS pregnancy patients (n=4). A noteworthy finding was that PAPS groups showed a higher proportion of impairment on a primary measure of executive functioning (DKEFS Trail Making 4) and verbal/auditory memory (BIRT Story Recall) compared to other outcomes.

Although an association between executive functioning and memory is recognised, differential patterns and associations between clinical populations is unclear (O'Brien et al., 2009). The implications for impairment in executive function include difficulties in planning, initiation, sequencing and monitoring of complex goal directed behaviour (Stuss & Alexander, 2000). As such, individuals may struggle to be independent, constructively self-serving and productive (Lezak, 2004). Impairments or mild deficits in this domain have been found to predict decline in disability and are associated with poor quality of life (Klein et al., 2003); poor HRQoL and the relationship between HRQoL in both the domains of executive function and memory is further evidenced in this study.

An assessment of HRQoL using subscales and summary scores of the SF-36 revealed that PAPS patients were impaired on most domains of HRQoL. The extent of this impairment is consistent with studies in SLE patients (e.g. Fortin, et al., 1998; Gladman, Urowitz, Ong, Gough, & Mackinnon, 1996; Sweet et al., 2004; Wang et al., 2001), with scores for PAPS thrombosis patients ranging from 4- 49% lower than controls. This suggests that this clinical population may be having difficulties adjusting to the challenges PAPS presents to their life roles, social relationships and physical and psychological health (Brennan, 2001; Charmaz, 1983; Livneh & Antonak, 1997). PAPS thrombosis patients were impaired on both physical and mental subscales and summary scores. Where this group has a higher prevalence of cognitive impairment, the findings are consistent with those in studies with SLE and MS patients (Utset et al, 2006; Amato, 2001). PAPS pregnancy patients were impaired mainly on mental health subscales. This may relate to mental health problems which have been found to be associated with pregnancy losses (Beutel, Deckardt, & Weiner, 1995). There were significant differences between PAPS patients and controls on all physical subscales and only one mental health subscale, Vitality. This was surprising given findings from research in similar clinical populations, which has found significant differences on all subscales and summary scores (Tam et al., 2008). However, the scores on Role Emotional, Mental Health and the MCS of healthy controls were almost below cut off; this is important to consider when interpreting the findings.

This study offers an initial exploration of the relationship between neuropsychological functioning and HRQoL. It was hypothesised that these variables would be positively correlated. Although moderate in strength, some correlations were in the expected direction and are consistent with findings from previous research. There were fewer outcomes significantly correlated with HRQoL in PAPS pregnancy patients compared with the PAPS thrombosis patients. Executive functioning was associated with mental health in both groups,

which is consistent with findings in patients with SLE (Tam et al., 2008) as well as physical health, a finding supporting that of Cutajar et al. (2000). Memory (CSRMT-W) was associated with physical and mental health in PAPS pregnancy patients, including the physical and emotional impact that PAPS has on their ability to fulfil roles in life such as work and other activities. Role limitation due to mental health was also associated with memory (CSRMT-F) in PAPS thrombosis patients, supporting findings of Panopalis et al. (2007).

Although not strong, there were a number of significant negative correlations. Other potential confounding variables that may be associated with HRQoL were not addressed, such as disease activity, disease duration, illness related behaviours, coping style, social support (McElhone, Abbott, & Teh, 2006) and illness perceptions (Weinman, Petrie, Moss-Morris, & Horne, 1996). Subjective cognitive dysfunction may also be a variable associated with HRQoL (Vinck, Put, Arickx, & Medaer, 1997), particularly where patients overestimate their cognitive difficulties (Harrison & Ravdin, 2006). Although investigating these variables was beyond the scope of this study, they do warrant exploration.

Regarding the clinical significance of the findings, it is noted that the size of the effects in comparing PAPS patients with controls ranged from medium (.40) to large (1.9). These are comparable to effect sizes observed in studies of cognitive impairment in patients with SLE who test positive for aPL antibodies compared with controls (Denburg et al., 1997). Furthermore, the prevalence of impairment in PAPS patients is comparable to that identified in a number of studies in SLE with and without CNS involvement (Denburg & Denburg, 2003; Monastero et al., 2001). This patient group is acknowledged to have clinically significant deficits; these results highlight the clinical importance of cognitive deficits found in PAPS, particularly those with PAPS thrombosis. In addition, HRQoL in PAPS is poor and this too is comparable to other clinical populations, also highlighting the importance of a

broad range of psychological, social, physical and somatic factors associated with chronic illness that are impaired in PAPS, some of which are associated with deficits in executive function and memory.

Studies exploring psychological factors in patients with PAPS are few. As this clinical population is expected to grow (Kasthuri & Roubey, 2009), it is important to consider future research that can inform the development of treatment approaches. The limitations and challenges of this study highlight areas for methodological improvements in future studies as well as further variables to explore.

While this study incorporated comprehensive inclusion/exclusion criteria, laboratory testing for aPL antibodies at the time of neuropsychological assessment may have strengthened the findings as would Magnetic Resonance Imaging (MRI) data to confirm the presence of other clinical features of CNS involvement in the clinical sample. Although the sample size may be regarded as limitation of the study, these initial findings are of interest and suggest a larger scale study is warranted. It is also important to acknowledge potential confounding variables, as referred to above, which may have explained the variance in HRQoL. It would be of interest to explore these variables further although not necessarily in association with cognitive functioning.

This study highlights the challenges of conducting neuropsychological research where it can be burdensome for patients to complete such large batteries at one time while also including other variables. A further issue in conducting neuropsychological research involving large batteries concerns the resources available in terms of time and availability of professionals to administer assessments. This investigation included four assessors which has implications for reliability and as such is another limitation of this study. When considering this in future research, it would be prudent to address the importance of consistency in assessments and assessors such that studies are comparable and evidence is strengthened.

## Conclusion

In summary, significant associations between PAPS thrombosis patients and cognitive dysfunction were found; in particular general intellectual abilities have declined and there are deficits in executive functioning and visual memory. PAPS patients, particularly those with PAPS thrombosis, experience poor HRQoL; both physical and mental aspects of HRQoL were found to be associated with executive function and memory. These findings indicate the importance of monitoring cognitive functioning in this population in those with and without overt CNS involvement. It also emphasises the need for the provision of interventions such as cognitive rehabilitation and psychological therapies, both of which may facilitate improved adjustment and quality of life in patients with PAPS.

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**Section C**

Critical Appraisal Paper

Word Count:

1966 (plus an additional 178 words)

## Introduction

This critical review is structured to address four specific questions providing a reflective account of how involvement in this project has contributed to the researcher's skills and abilities and highlighted areas where further learning is necessary. The review also discusses further clinical applications and research for cognitive functioning and health related quality of life (HRQoL) in patients with primary Antiphospholipid syndrome (PAPS).

*What research skills have you learned and what research abilities have you developed from undertaking this project and what do you think you need to learn further?*

The salient learning experiences for me, included skills acquired in the processes of problem solving and formulation, reviewing existing work and conceptual thinking and working collaboratively with motivated and dedicated health professionals.

There has been little research in primary APS but there is some evidence suggesting cognitive impairment in PAPS based on similar clinical populations. The process of gaining knowledge about PAPS and then reviewing this evidence was complex as much of what had been written was by physicians for medical journals and books. Working through this to create a logical and coherent argument for the study and the methodology challenged and developed my critical and conceptual thinking skills far more than any other assignment I have done during training. I believe the medical details and complexities of APS contributed to this but it was a very fulfilling part of the work for me given my interest in health conditions.

Although communicating the reasons for the research has been a skill I have used throughout the project, there are some key events that were important for me in relation to this. At the beginning I had to apply for further funding for research resources by explaining the research and requesting support. These skills were further employed at the ethics review

where I discussed the details of the methodology more specifically and clarified concerns of the committee. The process gave me confidence that the research was valid and in discussing it I realised that I had the knowledge and ability required to take the project further.

Although challenging, the most enjoyable part of the project has been working collaboratively with other health professionals. Teamwork has been integral the success of the project. Initially, my role was to create a team, communicate the value of the research and involve professionals who could fulfil the role of providing expertise in PAPS and assist in recruitment of participants. This was achieved within a specific medical context where there was no direct input from psychology. Working alongside those medical professionals provided me with an opportunity to demonstrate the role psychology can have in a physical health service.

Once the project started, the most important aspect was communicating with team members regularly, taking the time to maintain good relationships with each of them and keeping them motivated to meet recruitment targets. This is vital in research, especially when individuals are busy with the many other aspects of their day to day work roles in busy services where recruitment is not always at the forefront of their minds. As well as regularly visiting the team, I attended team research meetings to present the project to all health professionals related to the service with the aim of increasing awareness of the project and the need for participants.

Juggling this project with the demands of placement and other assignments meant that my organisational skills were put to the test and being as organised as possible was the only way to ensure the project would run smoothly. I was surprised at the length of time it took to organise appointments with participants. Although this could be time consuming when participants had many questions or experiences they wished to share it was also hugely interesting and rewarding and I regarded it as a very important part of the process.

Coordinating meeting with participants with the availability of research assistants and having access to one set of testing equipment was challenging at times. I was, however, well supported by the research assistants who were vital to this project.

Managing the data and conducting the analysis is a key research skill. Understanding the appropriate statistical analyses for this study has been satisfying and has given me the confidence to attempt quantitative research with statistical analyses in future.

Disseminating the findings of the study has been a valuable exercise in developing the ability to communicate scientific findings and tailoring the communication of the findings to a variety of audiences including the participants, the trustees of the Hughes Syndrome Foundation and the ethics committee. In writing up this project I have gained skills in communicating the study in a style specific to what is expected in the presentation of scientific research. It has highlighted to me the significance and challenges of conducting research ethically and being responsible and accountable for your work as a researcher.

In terms of further learning I think the main areas lie in different methodologies and larger projects. This project was on a small scale and so the skills learned are within that context. Larger scale projects across a number of sites with many more participants and many more health professionals working as part of a team would be more demanding on many levels. However, the skills learned on this project are transferable and would inform my working on a larger project. In terms of other methodologies, this study was a cross-sectional study and as such I now have the skills to apply this methodology again. I hope that in the future I have the opportunity to learn other quantitative as well as qualitative methodologies.

*If you were able to do this project again what would you do differently and why?*

There are practical aspects of this study which may have helped the project run more efficiently which I would have done differently. Mainly having the use of only one set of tests meant that only one participant could be assessed at any one time. This restricted the

recruitment process which was not ideal given the timescale of the project. Another aspect related to this is the time I had available to be on site when medical staff were recruiting for the study. While I was not able to identify potential participants as I did not have access to their medical records, there are times when I believe it would have been helpful for me to be present more often during clinic hours when recruitment took place. Having a member of the research team with a dedicated role of discussing the project and answering queries of potential participants might have taken some pressure off the medical team members who had their professional roles to carry out as well as helping with the recruitment. An important learning point relating to the difficulties with recruitment is that when the project was being planned, the certainty about the pool of possible participants was considered to be ample for the sample size needed. Once the inclusion/exclusion criteria were applied, however, this pool decreased. In future, I will give this more consideration so that I can plan accordingly.

An aspect of the project that I struggled with relates to my concerns around ethical practice. The participants in this study were not offered feedback on their assessments. This was made clear to them before they consented to take part and this is line with ethical practice (British Psychological Society (BPS, 2004a; BPS, 2004b), nonetheless, some participants expressed their regret about this. Unfortunately, I did not have the resources to provide any reports but when 'debriefing' (BPS, 2004a) with participants about the experience of being assessed, I offered brief feedback about their performance. I also communicated to them that I was available to discuss it at any time should they wish to contact me with questions or concerns.

Another important change I would have made concerns MRI brain scans and laboratory testing. Had there been the time and resources I believe it would have been helpful to include MRI brain scan data to confirm central nervous system involvement in participants and to take blood tests for all participants at the time of the assessments. This would have

allowed a comparison to be made between the level of antiphospholipid antibodies in participants' blood and performance on the neuropsychological assessments. In doing so, this may have provided further information about the relationship between the antibodies and cognitive impairment in this clinical population.

*As a consequence of doing this study, would you do anything differently in regard to making clinical recommendations or changing clinical practice, and why?*

APS is a relatively recently discovered disease and as such there is scarce research relating to psychological correlates of the condition. However as a chronic illness there is much that can be learned from studies relating to other autoimmune and chronic diseases such as Systemic lupus erythematosus (SLE), Multiple Sclerosis and Cancer where there is evidence suggesting the value of psychological interventions (Brennan, 2001; Mitchell, Kemp, Benito-Leon & Reuber, 2010, Navarrete-Navarrete et al., 2010) . In view of this, I believe that there are some important clinical recommendations to make and changes to clinical practice that could be made to serve those with PAPS.

Given the challenges associated with coping with this disease, patients and their families may benefit from interventions that facilitate adaptive coping/functioning and address psychological distress associated with having or caring for someone with the disease. This may include i) supporting patients to be informed and knowledgeable about their condition ii) providing psychoeducation to promote healthy behaviours (e.g. medication and stress management) iii) encouraging patients to focus on and develop goals relating to their talents and abilities and iv) promoting attendance at patient forums and setting up support groups (Iverson, 1995).

In terms of neuropsychology, deficits in cognitive skills could be tracked over the course of the illness and considered in relation to pharmacological interventions.

Psychological interventions addressing strengths and weaknesses could be designed to promote optimal social, occupational and educational adjustment. Patients and their families may feel reassured to know that their experiences of poor memory and/or flexibility in thinking may be associated with PAPS as opposed to any other conditions or mental health problem.

In practice, I would recommend i) building relations within the service, ii) informing and educating physicians about the role psychology can provide by presenting the evidence base for psychological interventions with other clinical populations and iii) clarifying the referral pathway by which those with PAPS can access psychology.

*If you were to undertake further research in this area what would that research project seek to answer and how would you go about doing it?*

There is much scope for further investigation of cognitive functioning and HRQoL in this clinical population. I would be interested in carrying out a larger scale study with more cognitive assessments and more participants but if one considers the evidence from other studies with similar clinical populations there are many variables that may be associated with these two aspects of PAPS.

As HRQoL can be considered to be a measure of adjustment to chronic illness, I would seek to explore the length of time since the disease had been diagnosed and compare this with illness perceptions, coping strategies and HRQoL. In this I would seek to answer whether there is an association between the period an individual has lived with a diagnosis of disease, the extent to which they have adjusted to having the disease, the coping strategies they employ in their illness experience and how they perceive their illness affects their lives. This could also include measures of executive functioning to determine whether any deficits are associated with those variables.

Where some patients with PAPS may be referred for psychological input, it would be interesting to compare HRQoL in those who have and have not had psychological intervention. If there were enough participants who had received a particular model of therapy it would be useful to measure the effectiveness of that particular model versus another with this clinical population.

I would also undertake research with this population using qualitative methodologies. Where many patients with PAPS struggled to have their illness validated and the disease diagnosed, it would be useful to explore the experiences of individuals and the impact this struggle has had on their lives. These experiences would most likely relate to aspects considered within the concept of quality of life but would provide a different, perhaps more detailed understanding. Where such studies have not been done, this is a clinical population who may want their experiences to be recognised in this way. In my meeting with participants for this study, this is the impression I gained and I believe there would be real value in exploring this qualitatively. Furthermore it could potentially provide a basis from which to inform further studies employing quantitative methods e.g. using more specific and meaningful psychological measures.

Many of the procedures I went through for this project would be required for each of the research ideas described above. The practicalities would be similar but I believe one of the key aspects would be to ensure there is a research team motivated to pursue the study. My experience of those members from the service from which this project was based is that it is a service and research unit that is dedicated to research in the field and that they would fully support further investigations.

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**Section D**

Appendix of Supporting Material

## Appendix A

Electronic Search for Literature Review

The literature was reviewed in 2010 and 2011 using electronic databases, including PsycINFO, PUBMED, MEDLINE, CINAHL, Sciencedirect, EBSOhost and EMBASE to search for research articles published between 1980 and 2011. The following search terms were applied for literature pertaining to antiphospholipid syndrome, cognitive functioning and quality of life: antiphospholipid syndrome / antiphospholipid antibodies/ lupus/ SLE/ hughes syndrome AND cognitive dysfunction/ memory/ quality of life. Search terms applied for literature specific to chronic illness and health related quality of life included: chronic illness AND coping/adjustment/adaptation/health related quality of life. Search terms relating neurological conditions and health related quality of life included: neurological conditions/stroke/multiple sclerosis/tumours/ AND quality of life.

These search terms were applied to all published literature including peer-reviewed papers and chapters in books, published in English.

Abstracts of references were read and articles sought where the abstract indicated that the paper described an empirical investigation or theoretical discussion relevant to the area of antiphospholipid syndrome, cognitive functioning and quality of life. A manual search of reference lists was also conducted to identify further relevant literature.

## Appendix B

Approval Letter from Ethics Committee

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## Appendix C

Approval Letter from NHS R&D Department

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## Appendix D

Funding Application to Hughes Syndrome Foundation

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## Appendix E

Email Confirming Funding from the Hughes Syndrome Foundation

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**Appendix F**

Patient Information Sheet (TRUST LOGO HERE)

## PATIENT INFORMATION SHEET

**Study title:**

Difficulties with memory and thinking processes, and quality of life in Antiphospholipid Syndrome (APS)

You are being invited to take part in a research study for people with APS. Before taking part it is important that you understand why the research is being done and what taking part involves. Please read the following information carefully. Feel free to discuss it with relatives, friends or your GP if you wish. You can also contact the researcher directly if there is anything that you would like to discuss further. Please see page 3 for contact details.

**What is the purpose of the study?**
It has been found that many patients with APS complain of difficulties with remembering and learning new information in addition to slowness in their thinking. Research has also shown that patients with similar chronic illnesses experience difficulty in coping with their condition, finding it physically and emotionally challenging. We know these problems occur but information is lacking about the precise difficulties experienced.

By studying groups of sufferers of this disease we hope to find out several things. Firstly, we hope to determine what proportions of people with this condition are affected with memory and cognitive ('thinking') problems. Secondly we hope to learn whether there are any recurrent patterns of memory and cognitive difficulty, which are characteristic of APS. Thirdly we want to know the how those with APS might be affected physically and emotionally by their condition.

**Why have I been chosen?**
We need to recruit 45 participants in total. If you have been asked to take part it will be because you have been diagnosed with APS.

**Do I have to take part?**
No, it is up to you whether you take part of not. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw from the study at any time after having agreed to take part, without giving any reason. This will not affect your care or your entitlement to any support offered within your service.

**What will happen to me if I decide to take part? What will I be asked to do?**
Providing you are suitable for the study and agree to take part, your doctor will allocate you to a group with others with the same characteristics of APS as you (i.e. pregnancy complications group, or the thrombosis characteristics group). A researcher will contact you and ask you to return to the clinic at a convenient time to you. The researcher will not be told which group you are in i.e. the researcher will not be told whether you suffer from APS with thrombotic characteristics or pregnancy complications. It is important that you do not tell the researcher which group you are in as this could influence the results of the study.

When you attend the appointment at the clinic, it will be to spend some time (approximately 2.5 hours) with a researcher who will do a range of simple tests designed to look for memory problems and difficulties with thinking. The tests involve paper and pencil and simply looking at words and pictures and recalling information.

You will also be asked to complete a questionnaire booklet containing questions about your physical and emotional well-being, your thoughts and feelings about APS and about the way you generally cope with stressful situations. This booklet will take a maximum of 20 minutes to complete.

All participants will be similarly assessed. Your assessment will be one-to-one over one visit lasting approximately 2.5 hours in total for all the tests to be completed.

If you take part in this study, you will not have to change your medication and your usual treatment will not be affected in any way.

If you experience distress during the time you are with the researcher, professional help is available at XXXXX. The researcher will ensure you receive this help.

A letter will be sent to your GP by a member of the healthcare team to inform them that you are participating in this research.

**What are the possible disadvantages and risks of taking part?**
The main disadvantage to taking part is the time involved in travelling to and attending appointment to completing the assessments. A risk of taking part is the possibility that in completing the assessments you experience some difficult emotions around the impact APS might be having on your well-being.

**What are the possible benefits of taking part?**
There will be no immediate benefit from taking part. The information we get from the study will contribute to our knowledge around memory and cognitive processes for APS patients and the impact APS has on your physical and emotional well-being. This information may help us to offer better support to APS patients.

**What if new information becomes available?**
Sometimes during the course of study, new information becomes available which impacts the condition that is being studied. If this happens the researchers will tell you about it and discuss with you whether you want to or should continue in the study. If you decide to withdraw, this will not influence the care you receive within the APS service. If you decide to continue you will asked to sign an updated consent form.

**What happens when the study stops?**
Once the study stops, there will be nothing further for you to do. Your care at XXXXX will not be impacted upon at any time during or after the study.

**Will my taking part in this study be kept confidential?**
Yes. All the questionnaires and information given by you will be confidential and coded to make it anonymous. This means that your name will not appear on any of your questionnaires. Questionnaires will be numbered and numbers will be linked to your name on a password-protected file. All information collected about you during the study that leaves the clinic will be kept strictly confidential in accordance with the Data Protection Act 1998. Data from this study will be retained for 10 years and subsequently disposed of securely.

**What happens to the results of the study?**
The study will be written up for publication in scientific journals and/or may be presented at scientific conferences. You will not be identified in any publication of presentation. If you would like to know the results of the study, we can provide you with a summary sheet.

**Who is organising the research?**
The study is being conducted by Lucy Tinning, a Trainee Clinical Psychologist from Salomons: Canterbury Christ Church University clinical psychology training programme. The research is supervised by XXXXX from Salomons and XXX from XXXX NHS Trust.

**Who else can I speak to about this research to get independent advice?**
You can speak with a member of the Hughes Syndrome Foundation organisation. Their contact details are:

Telephone:
Email:
Contact:

**Contact for further information**
If you would like to discuss your potential involvement further please contact:

**Name:**Lucy Tinning
**Job title:** Trainee Clinical Psychologist
**Telephone number:**
**Email address:**
**Address:**
Department of Applied Psychology
Canterbury Christ Church University
Salomons Campus
Broomhill Road
Tunbridge Wells
Kent
TN3 0TG

**If I decide to take part and want to make a complaint at any time, who can I contact?**
You can talk to the hospital's Patient Advice and Liaison Service (PALS), which provides support to patients, their families and visitors. Please ask a member of staff to direct you to their office or you can call xxx for the PALS team at XXXXX .

If you are not satisfied with the response that you receive, you can make a formal complaint in the following ways:

- Telephone the complaints department on
- Email your complaint to
- Write to the Chief Executive, at the address below
- Write to the complaints department at the address below

Address:
XXXXXX

***In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Canterbury Christ Church University and or XXXXX NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).***

**If I decide to take part and I experience distress and wish to seek support, who can I contact?**

You can seek support from The Hughes Syndrome Foundation (contact details provided on page 3) or you can seek help from your GP.

If you experience distress during the time you are with the researcher, professional help is available at XXXX. The researcher will ensure you receive this help.

**Who has reviewed this study?**
All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by XXXX Research Ethics Committee.

## Thank you for taking the time to read this information sheet

(TRUST LOGO HERE)

## PARTICIPANT INFORMATION SHEET

**Study title:**

Difficulties with memory and thinking processes, and quality of life in Antiphospholipid Syndrome (APS)

You are being invited to take part in a research study for people with APS. Before taking part it is important that you understand why the research is being done and what taking part involves. Please read the following information carefully. Feel free to discuss it with relatives, friends or your GP if you wish. You can also contact the researcher directly if there is anything that you would like to discuss further. Please see page 3 for contact details.

**What is the purpose of the study?**
It has been found that many patients with APS complain of difficulties with remembering and learning new information in addition to slowness in their thinking. Research has also shown that patients with similar chronic illnesses experience difficulty in coping with their condition, finding it physically and emotionally challenging. We know these problems occur but information is lacking about the precise difficulties experienced.

By studying and comparing groups of sufferers of this disease and those without the disease we hope to find out several things. Firstly, we hope to determine what proportions of people with this condition are affected with memory and cognitive ('thinking') problems. Secondly we hope to learn whether there are any recurrent patterns of memory and cognitive difficulty, which are characteristic of APS. Thirdly we want to know the how those with APS might be affected physically and emotionally by their condition.

**Why have I been chosen?**
We need to recruit 45 participants in total. Twenty participants include those who do not have APS. If you have been asked to read this information sheet, it will be because you do not have APS.

**Do I have to take part?**
No, it is up to you whether you take part of not. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw from the study at any time after having agreed to take part, without giving any reason.

What will happen to me if I decide to take part? What will I be asked to do?
Providing you are suitable for the study and agree to take part, the researcher will contact you and ask you to return to the clinic at XXXX at a convenient time to you. When you attend the appointment at the clinic, it will be to spend some time (approximately 2.5 hours) with a researcher who will do a range of simple tests designed to look for memory problems and difficulties with

thinking. The tests involve paper and pencil and simply looking at words and pictures and recalling information.

You will also be asked to complete a questionnaire booklet containing questions about your physical and emotional well-being. This booklet will take a maximum of 20 minutes to complete.

All members of the groups will be similarly assessed. Your assessment will be one-to-one over one visit lasting approximately 2.5 hours in total for all the tests to be completed.

If you experience distress during the time you are with the researcher, professional help is available at XXXXX Hospital. The researcher will ensure you receive this help.

**What are the possible disadvantages and risks of taking part?**
The main disadvantage to taking part is the time involved in travelling to and attending appointment to completing the assessments.

**What are the possible benefits of taking part?**
There will be no immediate benefit from taking part. The information we get from the study will contribute to our knowledge around memory and cognitive processes for APS patients and the impact APS has on their physical and emotional well-being. This information may help us to offer better support to APS patients.

**What if new information becomes available?**
Sometimes during the course of study, new information becomes available which impacts the condition that is being studied. If this happens the researchers will tell you about it and discuss with you whether you want to continue in the study. If you decide to continue you will asked to sign an updated consent form.

**What happens when the study stops?**
Once the study stops, there will be nothing further for you to do**.**

Will my taking part in this study be kept confidential?
Yes. All the questionnaires and information given by you will be confidential and coded to make it anonymous. This means that your name will not appear on any of your questionnaires. Questionnaires will be numbered and numbers will be linked to your name on a password-protected file. All information collected about you during the study that leaves the clinic will be kept strictly confidential in accordance with the Data Protection Act 1998. Data from this study will be retained for 10 years and subsequently disposed of securely.

**What happens to the results of the study?**
The study will be written up for publication in scientific journals and/or may be presented at scientific conferences. You will not be identified in any publication of presentation. If you would like to know the results of the study, we can provide you with a summary sheet.

**Who is organising the research?**
The study is being conducted by Lucy Tinning, a Trainee Clinical Psychologist from Salomons: Canterbury Christ Church University clinical psychology training programme. The research is supervised by XXXX from Salomons and XXXXX from XXXXX.

**Who else can I speak to about this research to get independent advice?**
You can speak with a member of the Hughes Syndrome Foundation organisation. Their contact details are:

Telephone:
Email:
Contact:

**Contact for further information**
If you would like to discuss your potential involvement further please contact:

**Name:**Lucy Tinning
**Job title:** Trainee Clinical Psychologist
**Telephone number**
**Email address:**
**Address:**
Department of Applied Psychology
Canterbury Christ Church University
Salomons Campus
Broomhill Road
Tunbridge Wells
Kent
TN3 0TG

**If I decide to take part and want to make a complaint at any time, who can I contact?**
You can talk to the hospital's Patient Advice and Liaison Service (PALS), which provides support to patients, their families and visitors. Please ask a member of staff to direct you to their office or you can call XXX for the PALS team at XXXXX.

If you are not satisfied with the response that you receive, you can make a formal complaint in the following ways:

- Telephone the complaints department on
- Email your complaint to
- Write to the Chief Executive, at the address below
- Write to the complaints department at the address below

Address:

***In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Canterbury Christ Church University and or XXXX NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).***

**If I decide to take part and I experience distress and wish to seek support, who can I contact?**
You can seek support from The Hughes Syndrome Foundation (contact details provided on page 3) or you can seek help from your GP.

If you experience distress during the time you are with the researcher, professional help is available at XXXX. The researcher will ensure you receive this help.

**Who has reviewed this study?**
All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by XXXX Research Ethics Committee.

## Thank you for taking the time to read this information sheet

**Appendix H**

Consent form for Patients and Healthy Control Participants

(TRUST LOGO)

## PATIENT CONSENT FORM

## CONSENT FORM FOR RESEARCH STUDY

**Title of Project:** Difficulties with memory and thinking processes, and quality of life in Antiphospholipid Syndrome (APS)

**Name of Researcher: Lucy Tinning**

| | **Please tick to confirm** |
|---|---|
| **I confirm that I have read and understand the information sheet for the above study.** | **-----** |
| **I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.** | **-----** |
| **I have been given full information regarding the aims of the research and have been given information with the researcher's name on and a contact number and address if I require further information.** | **-----** |
| **I understand that all personal information provided by myself to the researchers and clinician will remain confidential and no information that identifies me will be made publically available** | **-----** |
| **I agree to take part in the above research study.** | **-----** |

| **Name of Participant** | **Date** | **Signature** |
|---|---|---|
| _____ | _____ | _____ |
| **Researcher** | **Date** | **Signature** |

**Appendix I**

Template Letter to Patients' GP re. Participating in the Research

(NHS TRUST LOGO)
Hospital address

(Date)

**RE Name/DOB**

Dear Dr

This letter is to notify you that (patient) has decided to participate in the research study below:

**Difficulties with memory and thinking processes, and quality of life in Antiphospholipid Syndrome (APS)**

This research is based at Xxxxxx, London.

If you have any concerns about this, please do not hesitate to contact me.

Yours sincerely

Dr (Name of Consultant or Research Nurse)

**Appendix J**

Cover Letter to Participants re. Summary of Research Findings


Centre for Applied Social & Psychological Development

Clinical Psychology Programme
Broomhill Road
Tunbridge Wells
Kent
TN3 0TG

[Participant name]
[Participant address]

13th July 2011

Dear Ms [Participant surname]

Re. Your participation in my research project entitled:

**"Difficulties with memory and thinking processes, and quality of life in Antiphospholipid Syndrome"**

I would like to thank you again for participating in this research project – your participation was enormously valuable and Karen, Hannah, Sabrina and I enjoyed meeting with you.

You indicated that you would like to be sent a summary of the research findings. I am writing to let you know that I have recently completed the research and I have therefore enclosed the summary with this letter.

Thank you again and I wish you all best for the future.

Yours sincerely

Lucy Tinning
Trainee Clinical Psychologist

## Appendix K

Summary of Research Findings for Participants

**Research Summary:**
Difficulties with memory and thinking processes, and quality of life in Antiphospholipid Syndrome

Researcher: Lucy Tinning, Trainee Clinical Psychologist,
Canterbury Christ Church University
Supervisors: Dr. Paul Camic, Professor Michael Kopelman

**Aims of the study:**

I was interested in investigating 1) whether there was a relationship between APS and memory and thinking problems and if so 2) what proportion of APS suffers had this experience and 3) whether there was a pattern to these difficulties. I was also interested know the how those with APS might be 4) affected physically and emotionally by their condition and 5) whether thinking and memory problems were associated with this.

**Participants:**

All together, 45 people took part in the research, 30 had APS. Fifteen were allocated to an 'APS - pregnancy complications' group and fifteen were allocated to an 'APS-thrombosis characteristics' group. There were fifteen participants who did not have APS or any other underlying health problems. Everyone was asked the same questions and completed the same questionnaires as you.

**Analysis of responses:**

You ticked boxes with numbers next to them to indicate your responses to questions about physical and emotional well being. The questions in this questionnaire provided scores across 8 domains of physical and emotional well being. You also did a range of tests designed to look for memory problems and difficulties with thinking. I added up scores on every test completed to gain a total score for each test for every person. Scores from those with APS were compared with those participants who did not have APS (the 'control' group), to identify if there were any differences between those with and without APS.

The statistical tests I used to explore the relationship between memory and thinking processes and physical and emotional wellbeing were based on everyone's total scores considered together. For this reason, all of the findings of the research related to everyone's responses as a whole, not just yours individually. This means that personal experience of memory and thinking and physical and emotional well-being may be different from the results described. If they are, please be assured that your responses to the questionnaires and tests were included in the analysis but on average; responses were consistent with the findings below.

**Findings:**

Results showed that people with 'APS - thrombosis characteristics' were twice as likely to experience memory and thinking problems compared to those with 'APS - pregnancy complications'. Furthermore, in comparison to those who do not have APS ('control' group participants), people with 'APS- thrombosis characteristics' did not perform as well on the tests of memory and processes that require flexible thinking, such as initiating and stopping actions, switching between different tasks and situations as well as skills related to moving muscle groups e.g. hand/finger muscles used for drawing. People with 'APS -thrombosis characteristics' also demonstrated decreased levels in their general intellectual abilities when compared to their abilities before they had APS.

Both APS groups demonstrated poor physical and emotional well-being. However, physical well-being was poorer. Participants considered their physical health to limit their physical functioning and perceived their general health status to be worse than those who did not have APS. APS participants experienced greater pain and perceived their activities or work to be limited by their physical health condition when compared with people who do not have APS. Both groups of people with APS also felt more tired and less energetic compared to people without APS – this is influenced by emotional and physical problems.

General intellectual abilities, memory and thinking processes were all associated with emotional wellbeing for 'APS - thrombosis characteristics' participants and thinking processes and memory were associated with physical well being in 'APS - pregnancy complications' participants.

I hope that you find this summary helpful, and I would like to highlight again how valuable your contribution to this study has been.

**Appendix L**
Research Ethics Committee Declaration for End of Study

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**Appendix M**

Cover Letter to NHS Ethics Committee re. Summary of Research Findings


Centre for Applied Social & Psychological Development

Clinical Psychology Programme
Broomhill Road
Tunbridge Wells
Kent
TN3 0TG

Mr David Ingram
Committee Chair
East London REC 2
2nd Floor, Burdett House
Mile End Hospital
Bancroft Road
London
E1 4DG

13th July 2011

Study Title: **Cognitive functioning and quality of life in patients with Antiphospholipid Syndrome**

REC Reference: **10/H0704/39**

Dear Mr Ingram

Thank you for granting the above research ethical approval on 13th July 2010. I am writing to inform you that the data collection for the above research study has now concluded. Please find enclosed a summary of the research and its findings.

Please do not hesitate to contact me if you require any further information.

Yours sincerely

Lucy Tinning
Trainee Clinical Psychologist
Email: ljt29@canterbury.ac.uk

**Appendix N**

Cover Letter to NHS R&D Department re. Summary of Research Findings


Centre for Applied Social & Psychological Development

Clinical Psychology Programme
Broomhill Road
Tunbridge Wells
Kent
TN3 0TG

[Contact in Department]
[NHS Trust] Research & Development Department
[R&D Department Address]

13th July 2011

Study Title: **Cognitive functioning and quality of life in patients with Antiphospholipid Syndrome**

REC Reference: **10/H0704/39**

Dear [Contact]

Thank you for granting the above research approval on 9th September 2010. I am writing to inform you that data collection for the study has now been concluded. Please find attached a summary of the research and its findings.

Please do not hesitate to contact me if you require any further information.

Yours sincerely

Lucy Tinning
Trainee Clinical Psychologist
Email: ljt29@canterbury.ac.uk

## Appendix O

Summary of Research Findings for Ethics Committee and R&D Departments

**Research Summary:**
Cognitive Functioning and Quality of Life in Patients
with Antiphospholipid Syndrome
**REC Reference:** 10/H0704/39

Researcher: Lucy Tinning, Trainee Clinical Psychologist,
Canterbury Christ Church University
Supervisors: Dr. Paul Camic, Professor Michael Kopelman

**Background and Aims:**

Antiphospholipid syndrome (APS) is an autoimmune disease and chronic illness characterised by thrombosis and recurrent pregnancy morbidity in association with laboratory blood tests confirming moderate-to-high titer antiphospholipid (aPL) antibodies and/or the presence of the lupus anticoagulant. It may occur as an isolated diagnosis, primary APS (PAPS), or it may be secondary, associated with other autoimmune disorders such as Systemic lupus erythematosus (SLE-related APS). A clinical feature of APS is cognitive dysfunction which may be a direct manifestation of central nervous system (CNS) involvement.

Previous research has suggested that patients with aPL antibodies, secondary APS and PAPS experience cognitive deficits which can vary from mild neurocognitive disorders to severe global dysfunction in the context of dementia. However, research in this area is limited and studies have mainly included SLE patients testing positive for aPL antibodies. Research distinguishing secondary APS and PAPS patients specifically is more limited and mainly anecdotal. Findings so far have not identified any consistent pattern of cognitive dysfunction although there are similarities in the deficits found. Deficits have been identified in patients with and without CNS involvement in the disease.

As an autoimmune disease, APS is a chronic illness and patients live with the condition without a prospect of cure. The range of clinical features of APS, including cognitive dysfunction, are likely to impact upon aspects of patients' health related quality of life (HRQoL), where they may be presented with changes in their life roles and social and familial relationships while they concurrently manage psychological distress, physical pain, ongoing medical treatment and restrictions in the activities of daily living.

Research exploring cognitive dysfunction in PAPS or the experience of illness using HRQoL measures could not be found at the time of this study. Findings of research exploring HRQoL in similar clinical populations, such as SLE, indicate that scores on HRQoL measures have been 30-40% lower than those reported by matched peers with all domains of HRQoL affected.

This study aimed to explore the relationship between cognitive functioning and HRQoL in patients with Primary Antiphospholipid Syndrome (PAPS). Further aims of this study were to establish the characteristics and prevalence of cognitive dysfunction and HRQoL in PAPS

**Study Design:**

A cross-sectional study was employed, utilising a quantitative design

**Participants:**

Thirty adult females with a diagnosis of Primary Antiphospholipid Syndrome were recruited from (Name of Service and Hospital), (NHS Trust Name). Fifteen participants had experienced pregnancy complications (No CNS involvement in the disease) and fifteen participants had experienced a thrombotic event (CNS involvement in the disease). Fifteen healthy females were also included as a control group.

**Procedure:**

Participants completed a range of self-report questionnaires and neuropsychological assessments designed to measure HRQoL and cognitive functioning across domains of general intelligence, executive functioning and memory. Statistical analyses were then conducted using the subscale and total scores on each measure for each participant.

**Results:**

Patients in the PAPS thrombosis group were twice as likely to be designated as cognitively impaired compared to patients in the PAPS pregnancy group. The findings also suggest that PAPS thrombosis patients had experienced a decrease in their general intellectual functioning compared to pre-morbid levels. This group also demonstrated lower performance on measures of memory and executive functioning

compared to healthy controls. PAPS pregnancy patients also performed more poorly on these measures compared to healthy controls although not significantly. Both groups demonstrated poor HRQoL across physical and mental subscales. Both groups were significantly more impaired in all physical domains and one mental domain of HRQoL compared to controls. Neuropsychological outcomes in general intellectual abilities, memory and executive functioning were significantly associated with mental HRQoL subscales in PAPS thrombosis and executive functioning and memory were significantly associated with physical HRQoL subscales in PAPS pregnancy.

**Conclusions:**

In terms of the clinical significance of the findings, the research suggests that the size of effects found are comparable to those observed in studies of cognitive impairment in patients with SLE who test positive for aPL antibodies. Furthermore, the prevalence of impairment in PAPS patients is comparable to that identified in a number of studies in SLE. This patient group is acknowledged to have clinically significant deficits; these results highlight the clinical importance of cognitive deficits found in PAPS, particularly those with PAPS thrombosis. In addition, HRQoL in PAPS is poor and this too is comparable to other clinical populations, also highlighting the importance of a broad range of psychological, social, physical and somatic factors associated with chronic illness that are impaired in PAPS, some of which are associated with deficits in executive function and memory.

It is important to acknowledge potential confounding variables, such as disease activity, disease duration, coping style, social support and illness perceptions which may have explained the variance in HRQoL. When considering this in future research, it would also be prudent to address the importance of consistency in assessments such that studies are comparable and evidence is strengthened.

The findings indicate the importance of monitoring cognitive functioning in this population in those with and without overt CNS involvement. It also emphasises the need for the provision of interventions such as cognitive rehabilitation and psychological therapies, both of which may facilitate improved adjustment and quality of life in patients with PAPS.

Lucy Tinning
Trainee Clinical Psychologist

**Appendix P**

Cover Letter to the Hughes Syndrome Foundation re. Summary of Research Findings


Centre for Applied Social & Psychological Development

Clinical Psychology Programme
Broomhill Road
Tunbridge Wells
Kent
TN3 0TG

Hughes Syndrome Foundation
[Address]

13th July 2011

Study Title: **Cognitive functioning and quality of life in patients with Antiphospholipid Syndrome**

Dear Trustees

Thank you very much indeed for providing funding for the above research on 16th June 2010. I am writing to inform you that data collection for the study has now been concluded. Please find attached a summary of the research and its findings.

Please do not hesitate to contact me if you require any further information.

Yours sincerely

Lucy Tinning
Trainee Clinical Psychologist
Email: ljt29@canterbury.ac.uk

## Appendix Q

Summary of Research Findings for the Hughes Syndrome Foundation

### Research Summary:
### Cognitive Functioning and Quality of Life in Patients with Antiphospholipid Syndrome

Researcher: Lucy Tinning, Trainee Clinical Psychologist,
Canterbury Christ Church University
Supervisors: Dr. Paul Camic, Professor Michael Kopelman

**Background and Aims:**

A clinical feature of Antiphospholipid syndrome (APS) is cognitive dysfunction which may be a direct manifestation of central nervous system (CNS) involvement. Previous research has suggested that patients with aPL antibodies, APS and secondary APS (e.g. Systemic lupus erythematosus (SLE)-related APS) experience cognitive deficits which can vary from mild neurocognitive disorders to severe global dysfunction in the context of dementia. However, research in this area is limited and studies have mainly included SLE patients testing positive for aPL antibodies. Research distinguishing APS and secondary APS specifically is more limited and mainly anecdotal. Findings so far have not identified any consistent pattern of cognitive dysfunction although there are similarities in the deficits found. Deficits have been identified in patients with and without known CNS involvement in the disease.

As an autoimmune disease, APS is a chronic illness and the range of clinical features of APS, including cognitive dysfunction, are likely to impact upon aspects of patients' health related quality of life (HRQoL). Patients may be presented with changes in their life roles and social and familial relationships while they concurrently manage psychological distress, physical pain, ongoing medical treatment and restrictions in the activities of daily living.

Research exploring cognitive dysfunction in APS or the experience of illness using HRQoL measures could not be found at the time of this study. Findings of research exploring HRQoL in similar clinical populations, such as SLE, indicate that scores on HRQoL measures have been 30-40% lower than those reported by matched peers with all domains of HRQoL affected.

This study aimed to explore relationship between cognitive functioning and HRQoL in patients with APS. Further aims of this study were to establish the

characteristics and prevalence of cognitive dysfunction and HRQoL in patients with APS.

**Study Design:**

A cross-sectional study was employed, utilising a quantitative design

**Participants:**

Thirty adult females with a diagnosis of APS were recruited from (Name of Service and Hospital), (NHS Trust Name). Fifteen participants had experienced pregnancy complications (with no known CNS involvement in the disease) and fifteen participants had experienced a thrombotic event (and are likely to have CNS involvement in the disease). Fifteen healthy females were also included as a control group. Patients with secondary APS were excluded from this study.

**Procedure:**

Participants completed a range of self-report questionnaires and neuropsychological assessments designed to measure HRQoL and cognitive functioning across domains of general intelligence, executive functioning and memory. Statistical analyses were then conducted using the subscale and total scores on each measure for each participant.

**Results:**

Patients in the PAPS thrombosis group were twice as likely to be designated as cognitively impaired compared to patients in the PAPS pregnancy group. The findings also suggest that PAPS thrombosis patients had experienced a decrease in their general intellectual functioning compared to pre-morbid levels. This group also demonstrated lower performance on measures of memory and executive functioning compared to healthy controls. APS pregnancy patients also performed more poorly on these measures compared to healthy controls although not significantly. Both groups demonstrated poor HRQoL across physical and mental subscales. Both groups were significantly more impaired in all physical domains and one mental domain of HRQoL compared to controls. Neuropsychological outcomes in general intellectual abilities, memory and executive functioning were significantly associated with mental

HRQoL subscales in APS thrombosis and executive functioning and memory were significantly associated with physical HRQoL subscales in APS pregnancy.

**Conclusions:**

In terms of the clinical significance of the findings, the research suggests that the size of effects found are comparable to those observed in studies of cognitive impairment in patients with SLE who test positive for aPL antibodies. Furthermore, the prevalence of impairment in APS patients is comparable to that identified in a number of studies in SLE. This patient group is acknowledged to have clinically significant deficits; these results highlight the clinical importance of cognitive deficits found in APS, particularly those with APS thrombosis. In addition, HRQoL in APS is poor and this too is comparable to other clinical populations, also highlighting the importance of a broad range of psychological, social, physical and somatic factors associated with chronic illness that are impaired in APS, some of which are associated with deficits in executive function and memory.

It is important to acknowledge potential confounding variables, such as disease activity, disease duration, coping style, social support and illness perceptions which may have explained the variance in HRQoL.

The findings indicate the importance of monitoring cognitive functioning in this population in those with and without overt CNS involvement. It also emphasises the need for the provision of interventions such as cognitive rehabilitation and psychological therapies, both of which may facilitate improved adjustment and quality of life in patients with APS.

Lucy Tinning
Trainee Clinical Psychologist

**Appendix R** Table 5A. Pearson or Spearman 1-tailed correlation between SF-36 subscales and neuropsychological outcomes

| | | SF-36 Physical Functioning[a] | | SF-36 Role Physical[a] | | SF-36 Bodily Pain[a] | | SF-36 General Health[a] | | SF-36 Vitality[b] | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cognitive Domain**/ Neuropsychological outcomes | $r$ / $r_s$ | PAPS Pregnancy | PAPS Thrombosis | PAPS Pregnancy | PAPS Thrombosis | PAPS Pregnancy | PAPS Thrombosis | PAPS Pregnancy | PAPS Thrombosis | PAPS Pregnancy | PAPS Thrombosis |
| **General Intelligence** | | | | | | | | | | | |
| WASI Vocabulary | *r* | -0.57 * | -0.44 | -0.53* | -0.31 | -0.46* | -0.37 | -0.44 | -0.31 | -0.48* | 0.01 |
| WASI Similarities | *r* | -0.17 | -0.11 | -0.24 | -0.34 | -0.21 | -0.05 | -0.12 | -0.11 | -0.11 | 0.07 |
| WASI Block Design | *r* | -0.38 | 0.03 | -0.30 | 0.30 | -0.18 | -0.29 | -0.24 | -0.15 | -0.48* | -0.17 |
| WASI Matrix Reasoning | *r* | 0.15 | -0.15 | 0.05 | 0.15 | 0.32 | -0.16 | 0.18 | -0.22 | 0.00 | -0.42 |
| WASI Verbal IQ | *r* | -0.49* | -0.34 | -0.49* | -0.36 | -0.43 | -0.31 | -0.42 | -0.30 | -0.41 | 0.02 |
| WASI Performance IQ | *r* | -0.18 | -0.01 | -0.18 | 0.25 | 0.04 | -0.24 | -0.05 | -0.19 | -0.33 | -0.28 |
| WASI Full-scale IQ | *r* | -0.49* | -0.28 | -0.49* | -0.10 | -0.32 | -0.38 | -0.36 | -0.33 | -0.55* | -0.11 |
| **Executive Functioning** | | | | | | | | | | | |
| WAIS Digit Symbol Coding | *r* | 0.37 | 0.11 | 0.50* | 0.07 | 0.31 | -0.05 | 0.22 | -0.19 | 0.14 | -0.20 |
| WAIS Digit Span | *r* | 0.35 | -0.33 | 0.41 | -0.13 | 0.38 | -0.04 | 0.52* | -0.34 | 0.29 | -0.21 |
| WAIS Symbol Search | $r_s$ | -0.26 | -0.07 | -0.07 | -0.10 | -0.29 | -0.17 | -0.51* | -0.22 | -0.59* | -0.37 |
| DKEFS Letter Fluency | *r* | -0.01 | -0.17 | -0.17 | -0.11 | 0.12 | 0.23 | 0.07 | -0.10 | -0.02 | 0.09 |
| DKEFS Category Fluency | *r* | -0.16 | -0.26 | -0.03 | -0.35 | -0.04 | -0.13 | -0.17 | -0.17 | -0.07 | -0.27 |
| DKEFS Category Switching Responses | *r* | -0.03 | -0.14 | -0.03 | 0.13 | 0.31 | 0.13 | 0.13 | 0.03 | -0.13 | -0.10 |
| DKEFS Category Switching Accuracy | *r* | -0.14 | -0.13 | -0.16 | 0.15 | 0.22 | 0.12 | 0.02 | -0.02 | -0.23 | -0.07 |
| DKEFS Trail Making 1 | $r_s$ | -0.05 | -0.11 | -0.29 | 0.07 | 0.09 | -0.19 | -0.33 | -0.12 | -0.01 | -0.05 |
| DKEFS Trail Making 2 | $r_s$ | 0.06 | -0.43 | 0.14 | -0.25 | 0.31 | -0.28 | 0.28 | 0.58* | 0.13 | 0.56* |
| DKEFS Trail Making 3 | $r_s$ | 0.03 | -0.31 | 0.09 | -0.08 | -0.09 | -0.09 | -0.15 | -0.39 | -0.04 | -0.41 |
| DKEFS Trail Making 4 | $r_s$ | 0.27 | -0.06 | 0.49* | -0.03 | 0.03 | -0.02 | 0.40 | 0.02 | 0.37 | -0.16 |
| DKEFS Trail Making 5 | $r_s$ | -0.42 | -0.12 | -0.30 | -0.17 | -0.21 | -0.31 | -0.23 | -0.44 | -0.02 | -0.40 |
| DKEFS Composite Score | $r_s$ | 0.17 | -0.42 | 0.34 | -0.18 | -0.05 | -0.11 | 0.31 | -0.47* | 0.25 | -0.47* |
| **Memory** | | | | | | | | | | | |
| Camden Memory Test Faces | $r_s$ | 0.50* | 0.34 | 0.59** | 0.31 | 0.20 | 0.39 | 0.19 | 0.39 | 0.22 | 0.41 |
| Camden Memory Test Words | $r_s$ | 0.32 | 0.11 | 0.28 | -0.04 | -0.11 | 0.07 | 0.05 | 0.03 | 0.09 | 0.14 |
| BIRT Story Recall Immediate | *r* | 0.03 | 0.00 | -0.04 | -0.19 | 0.15 | -0.04 | 0.40 | 0.28 | 0.03 | 0.01 |
| BIRT Story Recall Delayed | *r* | 0.03 | -0.25 | -0.01 | -0.22 | 0.23 | -0.22 | .470* | 0.08 | 0.06 | -0.16 |
| BIRT Figure Recall Immediate | *r* | 0.00 | -0.39 | -0.08 | 0.05 | 0.29 | -0.49* | 0.05 | -0.38 | 0.28 | -0.42 |
| BIRT Figure Recall Delayed | *r* | 0.04 | -0.13 | -0.04 | 0.13 | 0.28 | -0.49* | 0.06 | -0.37 | 0.39 | -0.41 |
| Graded Naming | $r_s$ | -0.43 | 0.26 | -0.46* | -0.16 | -0.94 | 1.45 | -0.30 | -0.40 | -0.59** | 0.40 |

[a:] PCS ; [b:] MCS

*** < .000; ** < .01; * <.05

**Appendix R** Table 5B. Pearson or Spearman correlation between SF-36 subscales and neuropsychological outcomes

| | | SF-36 Social Functioning[b] | | SF-36 Role Emotional[b] | | SF-36 Mental Health[b] | | SF-36 Physical Component Score | | SF-36 Mental Component Score | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cognitive Domain/** Neuropsychological outcomes | *r* / $r_s$ | PAPS Pregnancy | PAPS Thrombosis | PAPS Pregnancy | PAPS Thrombosis | PAPS Pregnancy | PAPS Thrombosis | PAPS Pregnancy | PAPS Thrombosis | PAPS Pregnancy | PAPS Thrombosis |
| **General Intelligence** | | | | | | | | | | | |
| WASI Vocabulary | *r* | -0.42 | -0.39 | 0.10 | -0.47* | -0.01 | -0.02 | -.060** | -0.17 | 0.07 | -0.17 |
| WASI Similarities | *r* | -0.09 | -0.26 | 0.22 | -0.28 | 0.31 | 0.29 | -0.29 | 0.05 | 0.30 | 0.01 |
| WASI Block Design | *r* | -0.42 | -0.12 | 0.29 | 0.48* | 0.00 | 0.00 | -0.36 | -0.02 | -0.01 | 0.21 |
| WASI Matrix Reasoning | *r* | 0.11 | -0.22 | 0.33 | .517* | -0.02 | -0.06 | 0.16 | -0.14 | 0.07 | 0.18 |
| WASI Verbal IQ | *r* | -0.35 | -0.35 | 0.16 | -0.38 | 0.10 | 0.07 | -0.57* | -0.08 | 0.16 | -0.09 |
| WASI Performance IQ | *r* | -0.23 | -0.14 | 0.43 | 0.58* | 0.01 | 0.00 | -0.17 | -0.07 | 0.06 | 0.26 |
| WASI Full-scale IQ | *r* | -0.43 | -0.35 | 0.36 | 0.03 | 0.07 | 0.09 | -0.55* | -0.08 | 0.14 | 0.10 |
| **Executive Functioning** | | | | | | | | | | | |
| WAIS Digit Symbol Coding | *r* | 0.32 | -0.35 | 0.35 | 0.39 | 0.17 | 0.12 | 0.36 | -0.12 | 0.12 | 0.11 |
| WAIS Digit Span | *r* | 0.11 | -0.04 | 0.11 | 0.41 | 0.33 | 0.50* | 0.41 | -0.13 | 0.09 | 0.59* |
| WAIS Symbol Search | $r_s$ | -0.29 | -0.15 | 0.31 | 0.24 | -0.08 | 0.01 | -0.34 | -0.12 | -0.12 | 0.15 |
| DKEFS Letter Fluency | *r* | -0.04 | 0.09 | 0.02 | -0.01 | -0.28 | 0.05 | 0.02 | -0.13 | -0.11 | 0.10 |
| DKEFS Category Fluency | *r* | -0.05 | - 0.58* | 0.34 | 0.09 | -0.03 | 0.35 | -0.14 | -0.20 | 0.13 | 0.16 |
| DKEFS Category Switching Responses | *r* | -0.25 | -0.07 | -0.23 | 0.37 | -0.48* | 0.26 | 0.17 | -0.06 | -.047* | 0.31 |
| DKEFS Category Switching Accuracy | *r* | -0.32 | -0.05 | -0.24 | 0.39 | -0.47* | 0.31 | 0.04 | -0.04 | -0.45* | 0.37 |
| DKEFS Trail Making 1 | $r_s$ | -0.12 | -0.05 | -0.31 | 0.29 | -0.05 | 0.33 | -0.09 | -0.28 | -0.17 | 0.51* |
| DKEFS Trail Making 2 | $r_s$ | -0.06 | -0.12 | 0.01 | 0.20 | 0.07 | -0.02 | 0.30 | -0.36 | -0.05 | 0.17 |
| DKEFS Trail Making 3 | $r_s$ | -0.06 | 0.10 | 0.05 | 0.29 | 0.28 | 0.18 | -0.08 | -0.41 | 0.00 | 0.38 |
| DKEFS Trail Making 4 | $r_s$ | 0.17 | -0.22 | 0.26 | 0.23 | 0.57* | 0.15 | 0.30 | -0.18 | 0.36 | 0.26 |
| DKEFS Trail Making 5 | $r_s$ | 0.00 | -0.22 | 0.25 | -0.09 | -0.04 | -0.06 | -0.40 | -0.16 | 0.21 | -0.05 |
| DKEFS Composite Score | $r_s$ | 0.22 | 0.06 | 0.28 | 0.17 | 0.37 | -0.03 | 0.14 | -0.44 | 0.33 | 0.18 |
| **Memory** | | | | | | | | | | | |
| Camden Memory Test Faces | $r_s$ | 0.28 | 0.55* | 0.20 | 0.41 | 0.07 | 0.38 | 0.32 | 0.56* | 0.03 | 0.47* |
| Camden Memory Test Words | $r_s$ | 0.16 | -0.23 | 0.60** | -0.34 | 0.48* | 0.11 | 0.00 | 0.11 | 0.45* | -0.16 |
| BIRT Story Recall Immediate | *r* | 0.06 | -0.03 | -0.06 | 0.07 | 0.09 | 0.00 | 0.10 | 0.05 | 0.06 | 0.57 |
| BIRT Story Recall Delayed | *r* | 0.06 | -0.19 | -0.09 | 0.03 | -0.01 | 0.01 | 0.16 | -0.12 | -0.01 | 0.07 |
| BIRT Figure Recall Immediate | *r* | -0.01 | -0.39 | -0.24 | 0.18 | 0.01 | -0.38 | 0.07 | -0.18 | 0.01 | -0.11 |
| BIRT Figure Recall Delayed | *r* | 0.17 | -0.47* | -0.05 | 0.45* | 0.14 | -0.05 | 0.07 | -0.14 | 0.23 | 0.12 |
| Graded Naming | $r_s$ | -0.25 | -0.02 | 0.26 | -0.26 | -0.22 | 0.18 | -0.33 | 0.38 | -0.11 | -0.10 |

[a:] PCS ; [b:] MCS

*** < .000; ** < .01; * <.05

## Appendix S

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

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## Appendix T

Wechsler Adult Intelligence Scale III (WAIS III $^{UK}$; Wechsler, 1998) - subtests:

i) Digit Symbol Coding ii) Digit Span iii) Symbol Search (pages 1- 2)

i) Digit Symbol Coding

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ii) Digit Span

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iii) Symbol Search (page 1)

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## Appendix U

The National Adult Reading Test (NART; Nelson, 1982)

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## Appendix V

Delis Kaplan Executive Function System (DKEFS; Delis, Kaplan & Kramer, 2001) Verbal Fluency Test

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## Appendix W

Delis Kaplan Executive Function System (DKEFS; Delis, Kaplan & Kramer, 2001) – Trail Making Test Conditions 1 to 5 (front pages)

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## Appendix X

Delis Kaplan Executive Function System (DKEFS; Delis, Kaplan & Kramer, 2001) Trail Making Test Score Form

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## Appendix Y

The Brain Injury and Rehabilitation Trust (BIRT) Memory and Information Processing Battery (BMIPB; Oddy, Coughlan & Crawford, 2007) – Story Recall Form 1

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## Appendix Z

The Brain Injury and Rehabilitation Trust (BIRT) Memory and Information Processing Battery (BMIPB; Oddy, Coughlan & Crawford, 2007) – Figure Recall Form 1

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## Appendix Z1

Camden Memory Tests - Short Recognition Memory Test for Words and Faces

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## Appendix Z2

Graded Naming Test (GNT; McKenna & Warrington, 1983)

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## Appendix Z3

Medical Outcomes Survey Short Form-36 (SF-36; Ware & Sherbourne, 1992)

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## Appendix Z4

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith1983)

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## Appendix Z5

Tests for Normal Distribution and Homogeneity of Variance

The distributions for each total scale and each subscale were identified by examining Kolmogorov-Smirnov test scores. Scores that were significant indicated that the distribution of the sample was significantly different from a normal distribution.

Homogeneity of variance was identified by examining Levene's test for each total scale and subscale. Significant tests indicate that variances differ significantly between the groups.

Significance in either of these tests suggests assumptions of normality and/or homogeneity of variance have been violated and that non-parametric tests are appropriate.

1). Demographic and Clinical Characteristics of the PAPS patients and Controls

**Kolmogorov-Smirnov Tests of Normality: Demographic and Clinical Characteristics**

| | Group | Kolmogorov-Smirnov | | |
|---|---|---|---|---|
| | | Statistic | df | Sig. |
| Age | PAPS Pregnancy | .121 | 15 | .200 |
| | PAPS Thrombosis | .196 | 15 | .125 |
| | Control | .248 | 15 | .014* |
| Premorbid Full Scale IQ - NART | PAPS Pregnancy | .183 | 15 | .188 |
| | PAPS Thrombosis | .241 | 15 | .019* |
| | Control | .144 | 15 | .200 |
| HADS Depression Score | PAPS Pregnancy | .141 | 15 | .200 |
| | PAPS Thrombosis | .143 | 15 | .200 |
| | Control | .231 | 15 | .031* |
| Number of Years Education | PAPS Pregnancy | .233 | 15 | .027* |
| | PAPS Thrombosis | .220 | 15 | .050 |
| | Control | .328 | 15 | .000* |

*** <.000; ** < .01; * <.05

**Levene's Test of Homogeneity of Variance: Demographic and Clinical Characteristics**

| | | Levene Statistic | df1 | df2 | Sig. |
|---|---|---|---|---|---|
| Age | Based on Mean | 4.861 | 2 | 42 | .013* |
| | Based on Median | 1.413 | 2 | 42 | .255 |
| | Based on Median and with adjusted df | 1.413 | 2 | 25.080 | .262 |
| | Based on trimmed mean | 3.999 | 2 | 42 | .026 |
| Premorbid Full Scale IQ using NART error score | Based on Mean | .841 | 2 | 42 | .439 |
| | Based on Median | .521 | 2 | 42 | .598 |
| | Based on Median and with adjusted df | .521 | 2 | 26.791 | .600 |
| | Based on trimmed mean | .749 | 2 | 42 | .479 |
| HADS Depression Score | Based on Mean | .741 | 1 | 28 | .397 |
| | Based on Median | .551 | 1 | 28 | .464 |
| | Based on Median and with adjusted df | .551 | 1 | 26.737 | .464 |
| | Based on trimmed mean | .756 | 1 | 28 | .392 |
| Number of years education | Based on Mean | 2.488 | 2 | 42 | .095 |
| | Based on Median | .634 | 2 | 42 | .535 |
| | Based on Median and with adjusted df | .634 | 2 | 29.398 | .537 |
| | Based on trimmed mean | 2.296 | 2 | 42 | .113 |

*** <.000; ** < .01; * <.05

2. Neuropsychological outcomes

*2a. Neuropsychological outcomes – General Intelligence*

**Kolmogorov-Smirnov Tests of Normality : WASI**

| | Group | Kolmogorov-Smirnov | | |
|---|---|---|---|---|
| | | Statistic | df | Sig. |
| WASI Vocabulary Scaled Score | PAPS Pregnancy | .194 | 15 | .133 |
| | PAPS Thrombosis | .176 | 15 | .200 |
| | Control | .210 | 15 | .073 |
| WASI Block Design Scaled Score | PAPS Pregnancy | .136 | 15 | .200 |
| | PAPS Thrombosis | .163 | 15 | .200 |
| | Control | .213 | 15 | .067 |
| WASI Similarities Scaled Score | PAPS Pregnancy | .228 | 15 | .057 |
| | PAPS Thrombosis | .180 | 15 | .200 |
| | Control | .128 | 15 | .200 |
| WASI Matrix Reasoning Scaled Score | PAPS Pregnancy | .222 | 15 | .200 |
| | PAPS Thrombosis | .197 | 15 | .122 |
| | Control | .185 | 15 | .175 |
| WASI Verbal IQ | PAPS Pregnancy | .119 | 15 | .200 |
| | PAPS Thrombosis | .140 | 15 | .200 |
| | Control | .203 | 15 | .095 |
| WASI Performance IQ | PAPS Pregnancy | .128 | 15 | .200 |
| | PAPS Thrombosis | .142 | 15 | .200 |
| | Control | .178 | 15 | .200 |
| WASI Full scale IQ | PAPS Pregnancy | .137 | 15 | .200 |
| | PAPS Thrombosis | .116 | 15 | .200 |
| | Control | .144 | 15 | .200 |

*** <.000; ** < .01; * <.05

**Levene's Test of Homogeneity of Variance: WASI**

| | | Levene Statistic | df1 | df2 | Sig. |
|---|---|---|---|---|---|
| WASI Vocabulary Scaled Score | Based on Mean | .696 | 2 | 42 | .504 |
| | Based on Median | .391 | 2 | 42 | .679 |
| | Based on Median and with adjusted df | .391 | 2 | 23.295 | .681 |
| | Based on trimmed mean | .446 | 2 | 42 | .643 |
| WASI Block Design Scaled Score | Based on Mean | .854 | 2 | 42 | .433 |
| | Based on Median | .972 | 2 | 42 | .387 |
| | Based on Median and with adjusted df | .972 | 2 | 28.571 | .390 |
| | Based on trimmed mean | .941 | 2 | 42 | .398 |
| WASI Similarities Scaled Score | Based on Mean | .225 | 2 | 42 | .799 |
| | Based on Median | .321 | 2 | 42 | .727 |
| | Based on Median and with adjusted df | .321 | 2 | 39.858 | .727 |
| | Based on trimmed mean | .241 | 2 | 42 | .787 |
| WASI Matrix Reasoning Scaled Score | Based on Mean | .012 | 2 | 42 | .988 |
| | Based on Median | .009 | 2 | 42 | .992 |
| | Based on Median and with adjusted df | .009 | 2 | 38.525 | .992 |
| | Based on trimmed mean | .014 | 2 | 42 | .986 |
| WASI Verbal IQ | Based on Mean | .624 | 2 | 42 | .541 |
| | Based on Median | .416 | 2 | 42 | .662 |
| | Based on Median and with adjusted df | .416 | 2 | 36.474 | .663 |
| | Based on trimmed mean | .597 | 2 | 42 | .555 |

*** <.000; ** < .01; * <.05

**Levene's Test of Homogeneity of Variance: WASI** *continued*

| | | Levene Statistic | df1 | df2 | Sig. |
|---|---|---|---|---|---|
| WASI Performance IQ | Based on Mean | .177 | 2 | 42 | .839 |
| | Based on Median | .204 | 2 | 42 | .816 |
| | Based on Median and with adjusted df | .204 | 2 | 37.846 | .816 |
| | Based on trimmed mean | .204 | 2 | 42 | .817 |
| WASI Full scale IQ | Based on Mean | 1.633 | 2 | 42 | .208 |
| | Based on Median | 1.420 | 2 | 42 | .253 |
| | Based on Median and with adjusted df | 1.420 | 2 | 41.501 | .253 |
| | Based on trimmed mean | 1.634 | 2 | 42 | .207 |

*** <.000; ** < .01; * <.05

*2b Neuropsychological outcomes – Executive Functioning*

**Kolmogorov-Smirnov Tests of Normality: WAIS subtests**

| | Group | Kolmogorov-Smirnov | | |
|---|---|---|---|---|
| | | Statistic | df | Sig. |
| WAIS Digit Symbol Coding Scaled Score | PAPS Pregnancy | .227 | 15 | .133 |
| | PAPS Thrombosis | .155 | 15 | .200 |
| | Control | .127 | 15 | .200 |
| WAIS Digit Span Scaled Score | PAPS Pregnancy | .209 | 15 | .076 |
| | PAPS Thrombosis | .175 | 15 | .200 |
| | Control | .167 | 15 | .200 |
| WAIS Symbol Search Scaled Score | PAPS Pregnancy | .212 | 15 | .067 |
| | PAPS Thrombosis | .242 | 15 | .018* |
| | Control | .175 | 15 | .200 |

*** <.000; ** < .01; * <.05

**Kolmogorov-Smirnov Tests of Normality: DKEFS Fluency Tests**

| | Group | Kolmogorov-Smirnov | | |
|---|---|---|---|---|
| | | Statistic | df | Sig. |
| DKEFS Letter Fluency Scaled Score | PAPS Pregnancy | .115 | 15 | .200 |
| | PAPS Thrombosis | .157 | 15 | .200 |
| | Control | .151 | 15 | .200 |
| DKEFS Category Fluency Scaled Score | PAPS Pregnancy | .150 | 15 | .200 |
| | PAPS Thrombosis | .184 | 15 | .183 |
| | Control | .211 | 15 | .071 |
| DKEFS Category Switching Responses Scaled Score | PAPS Pregnancy | .171 | 15 | .200 |
| | PAPS Thrombosis | .127 | 15 | .200 |
| | Control | .184 | 15 | .182 |
| DKEFS Category Switching Accuracy Scaled Score | PAPS Pregnancy | .204 | 15 | .094 |
| | PAPS Thrombosis | .158 | 15 | .200 |
| | Control | .122 | 15 | .200 |

*** <.000; ** < .01; * <.05

**Kolmogorov-Smirnov Tests of Normality: DKEFS Trail Making Tests**

| | Group | Kolmogorov-Smirnov | | |
|---|---|---|---|---|
| | | Statistic | df | Sig. |
| DKEFS Trail Making Condition 1 Scaled Score | PAPS Pregnancy | .175 | 15 | .200 |
| | PAPS Thrombosis | .310 | 15 | .000*** |
| | Control | .222 | 15 | .046* |
| DKEFS Trail Making Condition 2 Scaled Score | PAPS Pregnancy | .246 | 15 | .015* |
| | PAPS Thrombosis | .156 | 15 | .200 |
| | Control | .195 | 15 | .129 |
| DKEFS Trail Making Condition 3 Scaled Score | PAPS Pregnancy | .294 | 15 | .001** |
| | PAPS Thrombosis | .159 | 15 | .200 |
| | Control | .321 | 15 | .000*** |
| DKEFS Trail Making Condition 4 Scaled Score | PAPS Pregnancy | .208 | 15 | .079 |
| | PAPS Thrombosis | .234 | 15 | .027* |
| | Control | .186 | 15 | .171 |
| DKEFS Trail Making Condition 5 Scaled Score | PAPS Pregnancy | .152 | 15 | .200 |
| | PAPS Thrombosis | .177 | 15 | .200 |
| | Control | .241 | 15 | .019* |
| DKEFS Condtion 2 plus Condition 3 Scaled Composite Score | PAPS Pregnancy | .215 | 15 | .038* |
| | PAPS Thrombosis | .119 | 15 | .200 |
| | Control | .147 | 15 | .200 |

*** <.000; ** < .01; * <.05

**Levene's Test of Homogeneity of Variance: WAIS subtests**

| | | Levene Statistic | df1 | df2 | Sig. |
|---|---|---|---|---|---|
| WAIS Digit Symbol Coding Scaled Score | Based on Mean | 2.642 | 2 | 42 | .083 |
| | Based on Median | 2.104 | 2 | 42 | .135 |
| | Based on Median and with adjusted df | 2.104 | 2 | 18.726 | .150 |
| | Based on trimmed mean | 2.477 | 2 | 42 | .096 |
| WAIS Digit Span Scaled Score | Based on Mean | .307 | 2 | 42 | .737 |
| | Based on Median | .331 | 2 | 42 | .720 |
| | Based on Median and with adjusted df | .331 | 2 | 40.987 | .720 |
| | Based on trimmed mean | .290 | 2 | 42 | .750 |
| WAIS Symbol Search Scaled Score | Based on Mean | 1.081 | 2 | 42 | .348 |
| | Based on Median | .331 | 2 | 42 | .720 |
| | Based on Median and with adjusted df | .331 | 2 | 24.250 | .721 |
| | Based on trimmed mean | .849 | 2 | 42 | .435 |

**Levene's Test of Homogeneity of Variance: DKEFS Fluency Test**

| | | Levene Statistic | df1 | df2 | Sig. |
|---|---|---|---|---|---|
| DKEFS Letter Fluency Scaled Score | Based on Mean | 1.734 | 2 | 42 | .189 |
| | Based on Median | 1.601 | 2 | 42 | .214 |
| | Based on Median and with adjusted df | 1.601 | 2 | 40.011 | .214 |
| | Based on trimmed mean | 1.728 | 2 | 42 | .190 |
| DKEFS Category Fluency Scaled Score | Based on Mean | .249 | 2 | 42 | .781 |
| | Based on Median | .306 | 2 | 42 | .738 |
| | Based on Median and with adjusted df | .306 | 2 | 41.637 | .738 |
| | Based on trimmed mean | .233 | 2 | 42 | .793 |
| DKEFS Category Switching Responses Scaled Score | Based on Mean | 1.789 | 2 | 42 | .180 |
| | Based on Median | 1.256 | 2 | 42 | .295 |
| | Based on Median and with adjusted df | 1.256 | 2 | 19.241 | .307 |
| | Based on trimmed mean | 1.648 | 2 | 42 | .205 |
| DKEFS Category Switching Accuracy Scaled Score | Based on Mean | 2.084 | 2 | 42 | .137 |
| | Based on Median | 1.559 | 2 | 42 | .222 |
| | Based on Median and with adjusted df | 1.559 | 2 | 27.616 | .228 |
| | Based on trimmed mean | 1.862 | 2 | 42 | .168 |

**Levene's Test of Homogeneity of Variance: DKEFS Trail Making Tests**

| | | Levene Statistic | df1 | df2 | Sig. |
|---|---|---|---|---|---|
| DKEFS Trail Making Condition 1 Scaled Score | Based on Mean | 8.376 | 2 | 42 | .001* |
| | Based on Median | 1.854 | 2 | 42 | .169 |
| | Based on Median and with adjusted df | 1.854 | 2 | 16.522 | .188 |
| | Based on trimmed mean | 5.781 | 2 | 42 | .006* |
| DKEFS Trail Making Condition 2 Scaled Score | Based on Mean | 3.666 | 2 | 42 | .034* |
| | Based on Median | 2.989 | 2 | 42 | .061 |
| | Based on Median and with adjusted df | 2.989 | 2 | 20.765 | .072 |
| | Based on trimmed mean | 3.233 | 2 | 42 | .049* |
| DKEFS Trail Making Condition 3 Scaled Score | Based on Mean | 4.266 | 2 | 42 | .021* |
| | Based on Median | 2.932 | 2 | 42 | .064 |
| | Based on Median and with adjusted df | 2.932 | 2 | 19.510 | .077 |
| | Based on trimmed mean | 3.630 | 2 | 42 | .035* |
| DKEFS Trail Making Condition 4 Scaled Score | Based on Mean | 2.377 | 2 | 42 | .105 |
| | Based on Median | .835 | 2 | 42 | .441 |
| | Based on Median and with adjusted df | .835 | 2 | 30.244 | .444 |
| | Based on trimmed mean | 1.720 | 2 | 42 | .192 |
| DKEFS Trail Making Condition 5 Scaled Score | Based on Mean | 2.834 | 2 | 42 | .070 |
| | Based on Median | 2.606 | 2 | 42 | .086 |
| | Based on Median and with adjusted df | 2.606 | 2 | 25.185 | .094 |
| | Based on trimmed mean | 2.880 | 2 | 42 | .067 |

*** <.000; ** < .01; * <.05

*2c Neuropsychological outcomes - Memory*

## Kolmogorov-Smirnov Tests of Normality: BIRT Story and Figure Recall

| | Group | Kolmogorov-Smirnov | | |
|---|---|---|---|---|
| | | Statistic | df | Sig. |
| BIRT Story Recall Immediate Scaled Score | PAPS Pregnancy | .134 | 14 | .200 |
| | PAPS Thrombosis | .194 | 15 | .133 |
| | Control | .171 | 15 | .200 |
| BIRT Story Recall Scaled Score | PAPS Pregnancy | .161 | 14 | .200 |
| | PAPS Thrombosis | .209 | 15 | .076 |
| | Control | .200 | 15 | .108 |
| BIRT Figure Recall immediate Scaled Score | PAPS Pregnancy | .151 | 14 | .200 |
| | PAPS Thrombosis | .124 | 15 | .200 |
| | Control | .212 | 15 | .070 |
| BIRT Figure Recall Delayed Scaled Score | PAPS Pregnancy | .136 | 14 | .200 |
| | PAPS Thrombosis | .173 | 15 | .200 |
| | Control | .163 | 15 | .200 |

*** <.000; ** < .01; * <.05

## Kolmogorov-Smirnov Tests of Normality: Camden Memory Tests

| | Group | Kolmogorov-Smirnov | | |
|---|---|---|---|---|
| | | Statistic | df | Sig. |
| Camden Memory Test Words Scaled Score | PAPS Pregnancy | .510 | 14 | .000*** |
| | PAPS Thrombosis | .430 | 15 | .000*** |
| | Control | .514 | 15 | .000*** |
| Camden Memory Test Faces Scaled Score | PAPS Pregnancy | .510 | 14 | .000*** |
| | PAPS Thrombosis | .253 | 15 | .011* |
| | Control | .535 | 15 | .000*** |

*** <.000; ** < .01; * <.05

## Kolmogorov-Smirnov Tests of Normality: Graded Naming Tests

| | Group | Kolmogorov-Smirnov | | |
|---|---|---|---|---|
| | | Statistic | df | Sig. |
| Warrington McKenna Graded Naming Scaled Score | PAPS Pregnancy | .164 | 14 | .200 |
| | PAPS Thrombosis | .224 | 15 | .041* |
| | Control | .242 | 15 | .019* |

*** <.000; ** < .01; * <.05

## Levene's Test of Homogeneity of Variance: BIRT Story and Figure Recall

| | | Levene Statistic | df1 | df2 | Sig. |
|---|---|---|---|---|---|
| BIRT Story Recall Immediate Scaled Score | Based on Mean | .440 | 2 | 41 | .647 |
| | Based on Median | .450 | 2 | 41 | .641 |
| | Based on Median and with adjusted df | .450 | 2 | 40.579 | .641 |
| | Based on trimmed mean | .442 | 2 | 41 | .646 |
| BIRT Story recall Scaled Score | Based on Mean | 1.197 | 2 | 41 | .313 |
| | Based on Median | .431 | 2 | 41 | .653 |
| | Based on Median and with adjusted df | .431 | 2 | 39.361 | .653 |
| | Based on trimmed mean | 1.154 | 2 | 41 | .325 |
| BIRT Figure recall immediate Scaled Score | Based on Mean | 1.979 | 2 | 41 | .151 |
| | Based on Median | .925 | 2 | 41 | .405 |
| | Based on Median and with adjusted df | .925 | 2 | 17.147 | .415 |
| | Based on trimmed mean | 1.371 | 2 | 41 | .265 |
| BIRT Figure Recall Delayed Scaled Score | Based on Mean | 2.027 | 2 | 41 | .145 |
| | Based on Median | 1.063 | 2 | 41 | .355 |
| | Based on Median and with adjusted df | 1.063 | 2 | 31.088 | .357 |
| | Based on trimmed mean | 1.746 | 2 | 41 | .187 |

**Levene's Test of Homogeneity of Variance: Camden Memory Tests**

| | | Levene Statistic | df1 | df2 | Sig. |
|---|---|---|---|---|---|
| Camden Memory Test Words Scaled Score | Based on Mean | 4.638 | 2 | 41 | .015* |
| | Based on Median | 1.438 | 2 | 41 | .249 |
| | Based on Median and with adjusted df | 1.438 | 2 | 16.379 | .266 |
| | Based on trimmed mean | 2.880 | 2 | 41 | .068 |
| Camden Memory Test Faces Scaled Score | Based on Mean | 16.564 | 2 | 41 | .000*** |
| | Based on Median | 7.862 | 2 | 41 | .001** |
| | Based on Median and with adjusted df | 7.862 | 2 | 18.416 | .003** |
| | Based on trimmed mean | 14.645 | 2 | 41 | .000*** |

*** <.000; ** < .01; * <.05

**Levene's Test of Homogeneity of Variance: Graded Naming Test**

| | | Levene Statistic | df1 | df2 | Sig. |
|---|---|---|---|---|---|
| Warrington McKenna Graded Naming Scaled Score | Based on Mean | .042 | 2 | 41 | .959 |
| | Based on Median | .041 | 2 | 41 | .960 |
| | Based on Median and with adjusted df | .041 | 2 | 35.746 | .960 |
| | Based on trimmed mean | .052 | 2 | 41 | .950 |

3. SF-36 Subscales and Mental Component Score and Physical Component Score

**Kolmogorov-Smirnov Tests of Normality : SF-36**

| | Group | Kolmogorov-Smirnov[a] | | |
|---|---|---|---|---|
| | | Statistic | df | Sig. |
| SF 36 Physical Functioning Norms-Based score 0-100 | PAPS Pregnancy | .217 | 15 | .056 |
| | PAPS Thrombosis | .179 | 15 | .200 |
| | Control | .335 | 15 | .000*** |
| SF 36 Role Physical Norms Based score 0-100 | PAPS Pregnancy | .191 | 15 | .147 |
| | PAPS Thrombosis | .122 | 15 | .200 |
| | Control | .500 | 15 | .000*** |
| SF 36 Bodily Pain Norms Based score 0-100 | PAPS Pregnancy | .220 | 15 | .049* |
| | PAPS Thrombosis | .170 | 15 | .200 |
| | Control | .302 | 15 | .001** |
| SF 36 General Health Norms Based score 0-100 | PAPS Pregnancy | .185 | 15 | .176 |
| | PAPS Thrombosis | .225 | 15 | .039* |
| | Control | .172 | 15 | .200 |
| SF 36 Vitality Norms Based score 0-100 | PAPS Pregnancy | .152 | 15 | .200 |
| | PAPS Thrombosis | .197 | 15 | .123 |
| | Control | .163 | 15 | .200 |
| SF 36 Social Functioning Norms Based score 0-100 | PAPS Pregnancy | .229 | 15 | .033* |
| | PAPS Thrombosis | .232 | 15 | .029* |
| | Control | .355 | 15 | .000*** |
| SF 36 Role Emotional Norms Based score 0-100 | PAPS Pregnancy | .215 | 15 | .061 |
| | PAPS Thrombosis | .207 | 15 | .082 |
| | Control | .245 | 15 | .016* |
| SF 36 Mental Health Norms Based score 0-100 | PAPS Pregnancy | .125 | 15 | .200 |
| | PAPS Thrombosis | .151 | 15 | .200 |
| | Control | .162 | 15 | .200 |
| SF 36 Physical Component score | PAPS Pregnancy | .184 | 15 | .181 |
| | PAPS Thrombosis | .143 | 15 | .200 |
| | Control | .124 | 15 | .200 |
| SF 36 Mental Component score | PAPS Pregnancy | .147 | 15 | .200 |
| | PAPS Thrombosis | .120 | 15 | .200 |
| | Control | .241 | 15 | .019* |

* <.000; ** < .01; * <.05

**Levene's Test of Homogeneity of Variance: SF-36**

| | | Levene Statistic | df1 | df2 | Sig. |
|---|---|---|---|---|---|
| SF 36 Physical Functioning Norms Based score 0-100 | Based on Mean | 6.223 | 2 | 42 | .004* |
| | Based on Median | 4.086 | 2 | 42 | .024* |
| | Based on Median and with adjusted df | 4.086 | 2 | 21.821 | .031* |
| | Based on trimmed mean | 5.322 | 2 | 42 | .009* |
| SF 36 Role Physical Norms Based score 0-100 | Based on Mean | 7.658 | 2 | 42 | .001** |
| | Based on Median | 6.327 | 2 | 42 | .004** |
| | Based on Median and with adjusted df | 6.327 | 2 | 32.331 | .005** |
| | Based on trimmed mean | 7.961 | 2 | 42 | .001** |
| SF 36 Bodily Pain Norms Based score 0-100 | Based on Mean | 6.385 | 2 | 42 | .004** |
| | Based on Median | 2.595 | 2 | 42 | .087 |
| | Based on Median and with adjusted df | 2.595 | 2 | 35.536 | .089 |
| | Based on trimmed mean | 6.173 | 2 | 42 | .004** |
| SF 36 General Health Norms Based score 0-100 | Based on Mean | 11.349 | 2 | 42 | .000*** |
| | Based on Median | 4.485 | 2 | 42 | .017* |
| | Based on Median and with adjusted df | 4.485 | 2 | 29.232 | .020* |
| | Based on trimmed mean | 10.511 | 2 | 42 | .000*** |
| SF 36 Vitality Norms Based score 0-100 | Based on Mean | 2.506 | 2 | 42 | .094 |
| | Based on Median | 2.011 | 2 | 42 | .147 |
| | Based on Median and with adjusted df | 2.011 | 2 | 36.839 | .148 |
| | Based on trimmed mean | 2.355 | 2 | 42 | .107 |

*** <.000; ** < .01; * <.05

**Levene's Test of Homogeneity of Variance: SF-36** *continued*

| | | Levene Statistic | df1 | df2 | Sig. |
|---|---|---|---|---|---|
| SF 36 Social Functioning Norms Based score 0-100 | Based on Mean | 2.048 | 2 | 42 | .142 |
| | Based on Median | 1.270 | 2 | 42 | .291 |
| | Based on Median and with adjusted df | 1.270 | 2 | 33.577 | .294 |
| | Based on trimmed mean | 1.504 | 2 | 42 | .234 |
| SF 36 Role Emotional Norms Based score 0-100 | Based on Mean | 3.728 | 2 | 42 | .032* |
| | Based on Median | 1.672 | 2 | 42 | .200 |
| | Based on Median and with adjusted df | 1.672 | 2 | 25.730 | .208 |
| | Based on trimmed mean | 2.884 | 2 | 42 | .067 |
| SF 36 Mental Health Norms Based score 0-100 | Based on Mean | .381 | 2 | 42 | .686 |
| | Based on Median | .309 | 2 | 42 | .736 |
| | Based on Median and with adjusted df | .309 | 2 | 41.638 | .736 |
| | Based on trimmed mean | .405 | 2 | 42 | .670 |
| SF 36 Physical Component score | Based on Mean | 3.879 | 2 | 42 | .028* |
| | Based on Median | 2.207 | 2 | 42 | .123 |
| | Based on Median and with adjusted df | 2.207 | 2 | 21.346 | .135 |
| | Based on trimmed mean | 3.096 | 2 | 42 | .056 |
| SF 36 Mental Component score | Based on Mean | .167 | 2 | 42 | .847 |
| | Based on Median | .037 | 2 | 42 | .964 |
| | Based on Median and with adjusted df | .037 | 2 | 24.021 | .964 |
| | Based on trimmed mean | .038 | 2 | 42 | .962 |

*** <.000; ** < .01; * <.05

## Appendix Z6

Submission Guidelines for Journal: “Journal of Neuropsychology”

# Journal of Neuropsychology



### Author Guidelines

The Journal of Neuropsychology publishes theory-driven patient studies. The central brief is to learn more from patients with brain dysfunctions to gain a better understanding of brain-behaviour relationships and to help future patients. Important developments in neuropsychology will follow from a multidisciplinary approach embracing neighbouring fields such as developmental psychology, neurology, psychiatry, physiology, endocrinology, pharmacology and imaging science. The journal publishes group and case studies addressing fundamental issues concerning the cognitive architecture of the brain. In addition, the journal includes theory-driven studies regarding the epidemiology of specific deficits, new assessment tools, and the evaluation of treatment regimes.

The journal is committed to a fast and efficient turn-around of papers, aiming to complete reviewing in under 90 days. Submissions are processed via a web-based system and reviewers are required to complete their referee report within 28 days.

Papers will be evaluated by the Editorial Board and referees in terms of scientific merit, readability, and interest to a general readership.

1. Quality Control

The content, format, quality and ambition of the JNP as a major outlet for theory-driven neuropsychological studies is under constant review by the Consulting Editors:

• Kenneth M. Heilman (University of Florida College of Medicine, Gainesville, USA)

• Donald T. Stuss (Rotman Research Institute, Baycrest, University of Toronto, Canada)

• Giuseppe Vallar (University of Milan-Bicocca, Italy)

• Elizabeth Warrington (National Hospital for Neurology and Neurosurgery, London, UK)

2. Circulation

The circulation of the Journal is worldwide. Papers are invited and encouraged from authors throughout the world.

3. Paper formats and length

Research papers are full-length reports of original scientific investigations. Papers should normally be no more than 6000 words excluding abstract (maximum 250 words) and references. Multiple citations for a single point are usually duplicative and authors are urged to cite the best reference. The Editor retains discretion to publish longer papers.

Theoretical or review articles are full-length reviews of, or opinion statements regarding, the literature in a specific scientific area. They need not be exhaustive but should give an interpretation

of the state of research in a given field. They should normally be no more than 4000 words excluding abstract (maximum is 250 words) and references. The number of references should not exceed 40-45. Multiple citations for a single point are usually duplicative and authors are urged to cite the best reference. The Editor retains discretion to publish longer papers.

Brief communications are short reports of original research or case reports. They contain no more than 1500 words excluding abstract (maximum is 80 words), references, a total of up to three tables or figures, and no more than 10 references.

Fast-track papers are timely and relevant reports that, to the discretion of the Editor, are included in the issue following acceptance. Authors may ask that their submitted manuscripts are considered for fast-track.

Commentaries and rejoinders are short reactions to publications in JNP followed by an invited rejoinder from the original authors.

Special issues may be proposed to the Editor. The proposal should include a short description of the topic and a number of (possible) contributors. The same quality criteria apply as for other submissions.

4. Submission and reviewing

All manuscripts must be submitted via http://www.editorialmanager.com/jnp/. The Journal operates a policy of anonymous peer review.

5. Manuscript requirements

• Contributions must be typed in double spacing with wide margins. All sheets must be numbered.

• Manuscripts should be preceded by a title page which includes a full list of authors and their affiliations, as well as the corresponding author's contact details. A template can be downloaded here.

• Tables should be typed in double spacing, each on a separate page with a self-explanatory title. Tables should be comprehensible without reference to the text. They should be placed at the end of the manuscript with their approximate locations indicated in the text.

• Figures can be included at the end of the document or attached as separate files, carefully labelled in initial capital/lower case lettering with symbols in a form consistent with text use. Unnecessary background patterns, lines and shading should be avoided. Captions should be listed on a separate sheet. The resolution of digital images must be at least 300 dpi.

• All articles should be preceded by an Abstract (see point 3 for guidelines), giving a concise statement of the intention, results or conclusions of the article.

• For reference citations, please use APA style. Particular care should be taken to ensure that references are accurate and complete. Give all journal titles in full.

• SI units must be used for all measurements, rounded off to practical values if appropriate, with the imperial equivalent in parentheses.

• In normal circumstances, effect size should be incorporated.

• Authors are requested to avoid the use of sexist language.

• Authors are responsible for acquiring written permission to publish lengthy quotations, illustrations, etc. for which they do not own copyright.

For guidelines on editorial style, please consult the APA Publication Manual published by the American Psychological Association.

6. Supporting Information

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At the editors' discretion, colour figures can be provided for use in the journal. Good quality photographs will be considered for inclusion where they add substantially to the argument, to a maximum of three per article. These can be supplied electronically as TIF files scanned to at least 300dpi. If they are not printed in colour, then they can be reproduced in colour online and black and white in print.

9. Pre-submission English-language editing

Authors for whom English is a second language may choose to have their manuscript professionally edited before submission to improve the English. A list of independent suppliers of editing services can be found at http://authorservices.wiley.com/bauthor/english_language.asp. All services are paid for and arranged by the author, and use of one of these services does not guarantee acceptance or preference for publication.

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