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Visual, auditory, and divided attention ability in early stage relapsing remitting multiple sclerosis. An investigation using novel dual modality paradigms.

VOLUME ONE

(VOLUME TWO BOUND SEPARATELY)

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Finally, I would like to dedicate this portfolio to my wife Audrey and my daughter Ilona. Thank you for your love, support, and encouragement.

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Chapter 1: Audit Project

A retrospective audit of routine, soon, and urgent referral patterns to a West of Scotland Clinical Psychology Department

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Prepared in accordance with the guidelines for submission to

Clinical Psychology

(See Appendix 1.1 for contributor's notes)

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Abstract

An audit was carried out of 18 months of referrals received by the Renfrewshire Adult Clinical Psychology Service from 1st August 2003 to 31st January 2005. The purpose of this was to ascertain the number of routine, soon, and urgent referrals received and to investigate GP referral patterns in relation to soon and urgent referrals. Also, the question of whether age of patient is attributable to urgency was examined.

The majority of referrals received were from GPs and variation in referral patterns between GP practices and between individual GPs was found.

Younger patients accounted for the largest percentage of all soon and urgent referrals, though older patients were more likely to be referred as a priority referral.

Introduction

Referrals to the department of Clinical Psychology at Dykebar Hospital are received from various referral agents including GPs in Primary Care GP Practices, Psychiatrists, General Medical Consultants, and other agencies. The Adult Mental Health Clinical Psychology service is comprised of a multidisciplinary team including clinical psychologists, counsellors, and a cognitive behavioural therapist. The department serves a population of approximately 196,000 providing service to inpatients, general medicine, community mental health team, and outpatient clinics.

There is a large demand on the service and due to the large volume of referrals received a waiting list system operates within the department and the number of weeks a patient can wait to be seen varies, depending on where they live and how many referrals are received for that area. Waiting lists can be extensive and are commonly found within many clinical psychology departments in Scotland due to increasing referrals and shortage of staff (CAPISH, 1999). Many departments recognise that some referrals need to be seen faster than others and to ensure that referrals requiring more urgent attention from a psychologist are seen quicker, the department operates a priority system in their waiting list. This leads to a referral to the department being categorised or accepted as either a routine referral, a soon referral, or as an urgent referral. A routine referral may have a waiting time of anything between 30 – 50 weeks, a soon referral is generally seen within 12 weeks, and an urgent referral is generally seen within 4 weeks. This system allows a referring agent the opportunity to request a faster appointment for their patient if it is felt necessary.

Often, the referring agent will make a specific request for their referral to be either routine or to be considered for soon or urgent status; however not all referrals arrive with the status requested. The department operates a prioritization system where all referral requests are viewed by one of the three Grade B Consultant Clinical Psychologists working there and the referral is then accepted or not accepted and if accepted, categorized as either 'Routine, Soon, or Urgent' before being placed on the waiting list. Again, this categorizing determines how long a patient will have to wait before being seen for assessment by a Clinical Psychologist or other clinician.

It should be noted that there might be a small amount of discrepancy between a referring agent's request of referral priority and the Clinical Psychologist's final categorization.

For example, a request for an urgent status on a referral by a GP may be deemed to require a routine status after the Clinical Psychologist views the content of the referral. Further, a routine request may be 'promoted' to a priority status if further information is received from the referring agent that warrants this. However, the Clinical Psychologists that categorize the referrals accept all the referrals that are marked as routine by the referring agent as a 'routine' and no referrals are given a 'soon or urgent' code by the Clinical Psychologist unless the referring agent specifically asks for this. The Clinical Psychologists subjective view is that very few soon or urgent requests are 'demoted' to a routine referral. In this audit, any potential discrepancy between a referring agent's opinion of priority status and the Clinical Psychologist's categorization is not being investigated, though it is a question of interest. This audit aims to look retrospectively at all referrals received by the Department of Clinical Psychology over an 18-month time window, specifically

investigating 'soon and urgent' referral generations (i.e. referrals that are accepted by the Clinical Psychology dept as being soon or urgent) from Primary Care (GPs).

The rationale for this audit has a local context and reflects the interests of the Clinical Psychologists at Dykebar Hospital to ascertain the number and patterns of referrals from different sources and in particular to look at referrals from GPs. It is a factual 'load finding' exercise for administrative purposes to ascertain how many priority referrals the department has to accommodate. The soon and urgent generations from GPs in Primary Care and whether there is any change over time in the number of soon and urgents accepted, is of particular interest. For example, are some GP Practices higher referrers than others and are any GPs in particular requesting priority referrals?

This information can aid in monitoring soon and urgent requests and provide a profile of GP referrals to Clinical Psychology. It would also be of interest in knowing what characteristics of a referral are attributable to priority and the hypothesis that younger patient referrals are more likely to be priority referrals is explored. While the content of the referral is also likely to be linked with priority level (Turken, 1993) and is of interest, it is beyond the scope of this audit to look at this.

The following aim, objectives, and questions formed the basis of this audit.

Aim:

The main aim was to retrospectively examine referral patterns to the Dykebar Department of Clinical Psychology over an 18-month (3 x 6 month) time frame from 01st August 2003 to 31st January 2005. The 3 x 6 month time frames have been chosen to allow comparisons of referrals over time to be made and these are 01st August 2003 to 31st January 2004, 01st February 2004 to 31st July 2004, and 01st August 2004 to 31st January 2005. Further, data for a full calendar year was collated. Eighteen months provides a reasonable amount of referral data to analyse, while assuming that staffing numbers remain constant and GP Practices have not undergone major change.

Objectives:

The objectives were to:

- Examine the number of referrals from each referral agent.
- Calculate the number of different classes of referrals (i.e. number of routines/soons/urgents that are accepted).
- Investigate Primary Care (GP) referral patterns in terms of soon/urgent referral generations.
- Investigate patient age and relationship with soon/urgent status.

This audit explored six specific questions of interest:

1. What is the percentage of referrals in terms of different referral agents?

2. What percentage of referrals were accepted as Routine, Soon, and Urgent by the Clinical Psychology Dept?
3. Did Primary Care (GPs) refer more than other referral agents (e.g. Psychiatry) to Psychology dept?
4. Do different GP Practices in the divisional area refer more than other practices and is this related to size (number of GPs) within the practice?
5. Were there any differences in individual GPs patterns of Soon and Urgent referrals?
6. Are soon and urgent referrals related to the age of the patient?

Methodology

Argyll & Clyde NHS Information and Technology department at Dykebar Hospital ran a software program that gathered the retrospective data from two databases that referrals to the Department of Clinical Psychology are entered on to. The data was then transferred into a working database that allowed manipulation and analysis of the data.

There was a sample size of (n = 1017) referrals in total received within the 18 months being looked at, and for each referral the following variables were gathered:

- Unique anonymous identifier: e.g., 'Patient 1.....Patient n'
- Patient age at date of referral
- Referring Agent
- Referral Date
- GP Practice Code

- GP Code
- Referral Priority Status

Also, information regarding the number of different GP practices, number of GPs in each practice along with the patient sizes for each practice was obtained.

Ethical Issues:

All data were anonymised by the information and technology department before reaching the data analysis stage. Therefore patient confidentiality was intact at all times and no data were gathered by visiting the individual patient files.

The local research and audit unit within the NHS division was informed that the audit was taking place and an audit proposal was submitted to them. Ethical clearance was not required before the audit project took place.

Results

The following results relate to each individual audit question, previously stated in the methodology section.

Question 1: What was the percentage of referrals in terms of the different referring agents?

During the time frame being examined the department received 1017 referrals, with the majority of referrals 62.5% coming from GPs. The next largest referrer was psychiatry, which accounted for 28.2% of referrals. Table 1 displays the number of referrals received from each referral source across the different time frames being examined.

---------- Insert Table 1 here ----------

Question 2: What number of referrals were accepted as Routine, Soon, and Urgent by the Clinical Psychology Department?

The majority of referrals were accepted as routine (n = 853), with soon (n = 128), and urgent (n = 36). Figure 1 displays this in graphical form.

---------- Insert Figure 1 here ----------

Table 2 examines the number of priority referrals across the chosen time frames

---------- Insert Table 2 here ----------

In our sample, 83.9% of referrals were routine, and over the three six-month time frames the number of routine referrals accepted were similar. Soon referrals accounted for 12.6% of the sample and clearly fluctuated over time, with 61 soon referrals accepted in the first 6 months of our sample, dropping to 29 soon referrals accepted in the last 6 months of our sample. Thirty six (3.5%) of the sample were urgent referrals, and over time there is variation in the number of urgent referrals accepted.

Question 3: Did Primary Care (GPs) refer more than other referral agents to Clinical Psychology?

In total, 62.5% of referrals were received from GPs. This is more than double the percentage of referrals from psychiatry (28.2%) and psychiatry is the next biggest referral agency after GPs. This finding is consistent across all time frames examined. In terms of priority referrals, the highest amount of soon referrals (57%) come from GPs, and 44% of urgent referrals come from GPs, compared to 32% and 27.8% respectively for psychiatry soon and urgent referrals.

Question 4: Were there differences in referral numbers from different GP practices? Was there an association between number of referrals received from a practice and number of GPs within the practice?

The GP referrals were generated from four main sectors within the divisional area: Paisley, West Renfrewshire, Levern Valley, and Renfrew.

Very few referrals were received from Glasgow based GPs due to a minority of patients within the divisional area having a Glasgow based GP.

Figure 2 shows the number of GP referrals received from each sector.

---------- Insert Figure 2 here ----------

When comparing the number of GP referrals from each sector it is quite clear that different sectors refer more than others. Paisley sector refers the most (n = 328) and accounts for 51.6% of GP referrals. This sector has 13 different GP practices with a total number of 55 GPs and a patient list size of 83308 patients. The West Renfrewshire sector made 165 (26%) of the referrals and this sector has 16 different GP practices with a total number of 47 GPs and a patient list size of 80086 patients.

The Levern Valley sector accounts for 75 (11.8%) of GP referrals and has 4 different GP practices with a total number of 16 GPs and has a patient list size of 24800. The Renfrew sector made 52 (8.2%) of the GP referrals and has 3 different GP practices with a total number of 11 GPs and has a patient list size of 19473.

There are clear intersector differences in the number of GP referrals received and to investigate the association between number of GPs within a practice and number of referrals received a scattergram was produced (see Figure 3).

---------- Insert Figure 3 here ----------

The hypothesis was that there would be a positive association between the number of GPs within a GP practice and the number of referrals received from a practice. Informal inspection of the scattergram in Figure 3 shows that the number of referrals received tends to increase as the number of GPs within a practice increases, although there is a lot of variation present. The strength and direction of the correlation was formally tested using the non-parametric Spearman's Rho (r_s) and this was calculated as $r_s = 0.516$ which is statistically significant at the level of $p = 0.01$ (1 tailed). Therefore, there is a positive correlation between number of GPs within a practice and the number of referrals received from a practice and this association is moderately strong (Coolican, 1999).

A full anonymised breakdown of the number of referrals in total and across the 3 time frames from individual GP practices is given later with the corresponding number of GPs within each practice. It can be seen that in each sector some GP practices refer more than other practices, even when there are a similar number of GPs within the practices. For example, in the Levern Valley sector, two of the four GP practices each have six GPs and respectively referred 11 and 42 patients. In the Paisley sector, one GP practice with five GPs referred 47 patients, whereas a similar sized practice referred 16 patients.

Question 5: Were there any differences in individual GPs patterns of Soon and Urgent referrals?

Table 3 displays the number of GP soon and urgent referrals over the different time frames.

---------- Insert Table 3 here ----------

The 16 urgent referrals received in the 18 months were generated by eleven different GPs across eleven different GP practices, therefore, 8.5% of the total number of GPs within the divisional area, requested urgent referrals. Specifically, seven of the eleven GPs requested one urgent referral each, three GPs requested two urgent referrals each, and one GP requested three urgent referrals. The majority, 11 (68.7%) of the urgent requests came from GPs within Paisley sector practices with the highest amount of urgents (n = 4) from one specific Paisley GP practice, three of which were from one particular GP.

The 73 soon referrals were generated by twenty eight different GP practices and forty seven different GPs: 36% of GPs requested soon referrals. A GP practice in the Levern Valley sector requested the most number of soons (n = 7). One GP from a Paisley sector practice of the requested the most soon referrals (n = 4). Of the forty seven GPs who requested soon referrals 17 (36.2%) requested more than one soon over the 18 months. Also of interest, we can see overall that the number of GP soon and urgent referrals were both decreasing over time.

Question 6: Were soon and urgent referrals related to the age of the patient?

To investigate this question we examined all the referrals received for the following age bands: 1. Less than or equal to 25 years, 2. 26-35 years, 3. 36-45 years, 4. 46-55 years, 5. 56-65 years, 6. Over 65 years. Figure 4 shows the number of referrals received for each age band with proportions in each priority level.

---------- Insert Figure 4 here ----------

Subjectively, Figure 4 shows that most referrals were from patients in the age range of less than 25 years to 45 years, and as age increases, the number of referrals within the age band decreases. The number of soon and urgent referrals for the different age bands is shown in Table 4.

---------- Insert Table 4 here ----------

The age bands </= 25 years to 35 years account for 52.7% of all urgent referrals and 52.3% of all soon referrals. The 36 years to 55 years group account for 22.2% and 35.9% of all urgent and soon referrals respectively, and the 56 years and over group account for 25% of all urgent referrals and 11.7% of all soon referrals. It would appear that the majority of soon and urgent referrals were younger patients.

This was further investigated by calculating soon and urgent referrals together as a percentage of the total number of referrals for each age group to ascertain if a higher number of younger patient referrals received a priority status. In the 25years and under range, 16.5% of referrals were priority; 18% were priority in the 26-35 year range; 10.7% were priority in the 36-45 year range; 17% were priority in the 46-55 year range; 23.2% were priority in the 56-65 year range; and 21% were priority in the 65 years and over age range. These percentages are shown in Figure 5.

---------- Insert Figure 5 here ----------

In the </= 25 years to 35 years range, 34.5% of these referrals were priority referrals. In the 36 years to 55 years age range, 27.7% of these referrals were priority, and in the 56 years and over group 43.2% of these referrals were priority referrals. However, when interpreting these figures we must remember the different sample sizes within each age range and the effect of this on the relative proportions of priority referrals.

Discussion

The present audit aimed to examine all the referrals received by the Adult Clinical Psychology service during an 18-month time frame in order to quantify the numbers of referrals generated by different referral sources and also to look in particular at the referrals received from GPs. Also, this 'load finding' exercise was interested in determining the number of soon and urgent referrals the department has to accommodate and whether there are any relationships between soon and urgent referrals and GPs. Further, the age of the patient and any association with priority status was examined.

The majority of referrals received by the department were from GPs within the divisional area. In total, 62.5% of referrals from the sample were from GPs and this is considerably more than other referral sources including psychiatry. There are four main GP sectors that refer to the department, Paisley, West Renfrewshire, Levern Valley, and Renfrew. These sectors cover different population sizes, and Paisley, which has the largest patient size of 83308 patients, refers the most to the department and accounts for 51.6% of all GP referrals. Interestingly, the West Renfrewshire sector GP practices have a slightly less patient population size, being 80086 patients, however this sector accounts for 26% of all GP referrals; almost half of the number received from the Paisley sector. One reason for this may be that the Paisley GPs cover a dense urban population whereas the West Renfrewshire GPs cover a larger and more heterogeneous area. Verhaak (1993) examined what characteristics of the patient led to a mental health referral being made and found that increased urbanization led to an increase in referrals. The Levern Valley and Renfrew sectors

account for 11.8% and 8.2% of GP referrals respectively and these sectors have lower patient list sizes and a lower number of GPs working within the sectors.

There was a moderately strong association between the number of GPs within a practice and the number of referrals received from a practice, ($r_s = 0.516$) which is statistically significant at the level of $p = 0.01$ (1 tailed). However, Figure 3 shows that there is a lot of variation in this pattern, with some practices with similar numbers of GPs referring a disproportionably higher number of referrals. From the present study it is difficult to infer why this may be but some authors (Knight, 2003) have found that the GPs perceived ability to deal with patients who present with psychological difficulties affects their referral rate to specialist services. Hendryx, Doebbeling, and Kearns (1994) found that greater use of referral to a specialist service was made by GPs with low confidence in their ability to treat psychological problems. In an investigation of referral rates to a psychiatry service (Ashworth, Clement, Sandhu, Farley, Ramsay, and Davies, 2002) found a large variation in referral rates between GP practices and suggest that the variation in referral rates may relate to GP style: a "conduit" style where most mental health cases are referred to specialist services, and a "container" style, who offer primary care interventions.

The soon and urgent referrals received from GPs were analysed and it was found that GPs account for 54.4% of soon and urgent referrals combined, however less than half 44.5% of all the GPs within the divisional area requested a prioritized request. It was found that the majority of urgent requests came from the Paisley sector and one GP from the Paisley area requested the most urgent referrals. With soon referral requests, the majority were received from Paisley sector practices and one GP from a Paisley

GP practice requested the most soon referrals. This variation may be explained by the increased degree of urbanization within the Paisley sector and perhaps there is an association with degree of urbanization and complexity of patients with mental health problems that present to their GP. The most common mental health problems presented to GPs are depression and anxiety disorders (Goldberg & Huxley, 1992), however in larger urban areas patients may present with comorbid problems, leading to an increase in priority referral requests to clinical psychology. Shannon, Gillespie, McKenzie, and Murray (2001) suggest that when GPs are faced with long psychology waiting lists they will refer only the most severe cases to clinical psychology.

Further, there may be a lack of understanding by a GP as to what types of patient problems should be categorized as routine, soon, or urgent, leading to some referrers choosing the quickest possible route for their patient. Chadd and Svanberg (1994) surveyed GPs perceptions of clinical psychologists and found that long waiting lists led to a perception of inaccessibility to clinical psychology and that GPs value speed of response most. Paxton, Shrubb, Griffiths, Cameron, Maunder (2000) state that there is no widely accepted guidance for primary care with regards to thresholds for referral to secondary specialist services. It may be beneficial for the clinical psychology department to prepare and circulate guidelines about criteria for, and expected rates, of soon and urgent referrals, to GPs within the divisional area. Gray and Cogan (2002) found that specific criteria sent to GPs regarding urgency status were used more appropriately than broad criteria. O'Donnell (2000) found a large variation in GP referral rates and suggests that referral rates should be used to stimulate dialogue between primary care and secondary care to increase the appropriateness of referrals.

The relationship between age and priority level was further examined and in our sample the majority of soon and urgent referrals were accounted for by patients in the 35 years and under age group. Verhaak (1993) examined patient characteristics influencing referral to mental health services and found that younger patients had a greater probability of being referred.

It may be that patients in the younger age range are undergoing major life transitions with increased stress and vulnerabilities that lead to them being prioritized (Willis, 2005). Interestingly, (Willis, 2005) found that referral agencies do identify a significant need for clinical psychology among young adults, however, the younger adults in their sample showed low opt in, fewer initial attendances, and more failed appointments. This data may be useful when deciding whether to accept a priority referral in the younger adult age range. When we examined the percentage of priority referrals within an age range we found a greater relative number of younger and older patients being priority cases. In the 56 years and over age range, 43.2% of these referrals are priority referrals.

Conclusions

The implications of this audit are that it informs the clinical psychology staff of the number of referrals likely to be received from different sources and the likely percentage of referrals that will be soon or urgent referrals. This information can assist in managing waiting lists and stimulating discussion regarding production of priority guidelines for referrers. Future audits could assess level of agreement between referrers and psychologists rating of priority and referral characteristics attributable to urgency.

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List of tables and figures to be included in the main body of the report.

Table 1: Number of referrals from each referrer across 18-month time frame

Referral Agent	Time 1 (01/08/03-31/01/04)	Time 2 (01/02/04-31/07/04)	Time 3 (01/08/04-31/01/05)	12 Months (%) (01/01/04-31/12/04)	18 Months (%) (01/08/03-31/01/05)
GP	219	192	224	409 (61.5%)	**635 (62.5%)**
Psychiatry	108	105	74	192 (29.1%)	**287 (28.2%)**
General Medicine	24	22	15	37 (5.6%)	**61 (6%)**
Self Referral	4	6	5	10 (1.5%)	**15 (1.5%)**
Other Medical	5	4	3	7 (1.1%)	**12 (1.2%)**
Other Agency	2	1	4	6 (0.9%)	**7 (0.7%)**
Total	**362**	**330**	**325**	**661**	**1017**

Figure 1: Graph of number of referrals by priority status

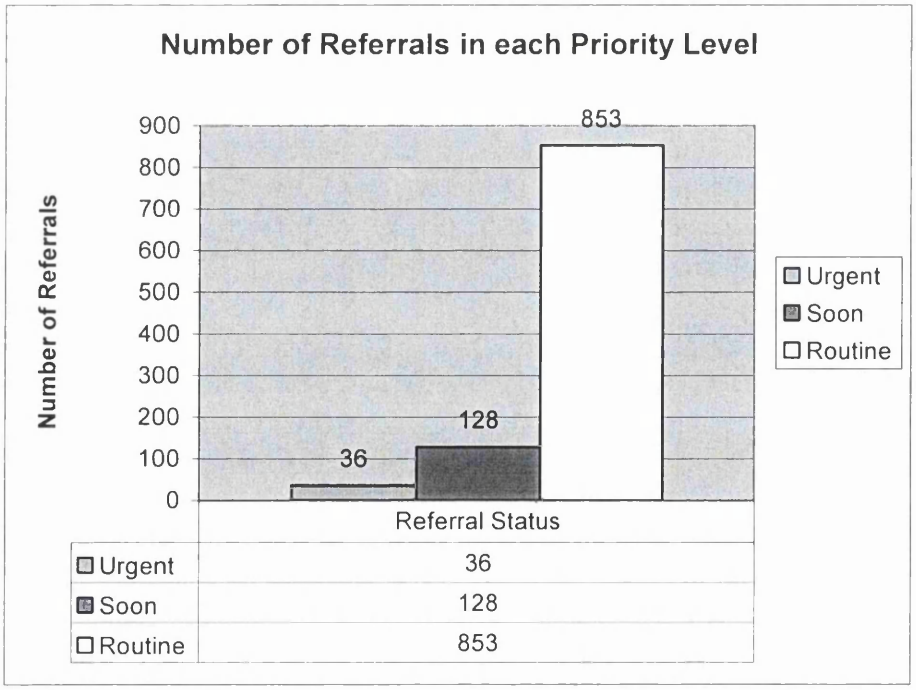


Table 2: Number of referrals by priority

Referral Priority Level	Time 1	Time 2	Time 3	12 Months (%)	18 Months (%)
Routine	283	284	286	572 (86.5%)	**853 (83.9%)**
Soon	61	38	29	71 (10.7%)	**128 (12.6%)**
Urgent	18	8	10	18 (2.7%)	**36 (3.5%)**
Total	**362**	**330**	**325**	**661**	**1017**

Figure 2: Graph of number of GP referrals from each sector

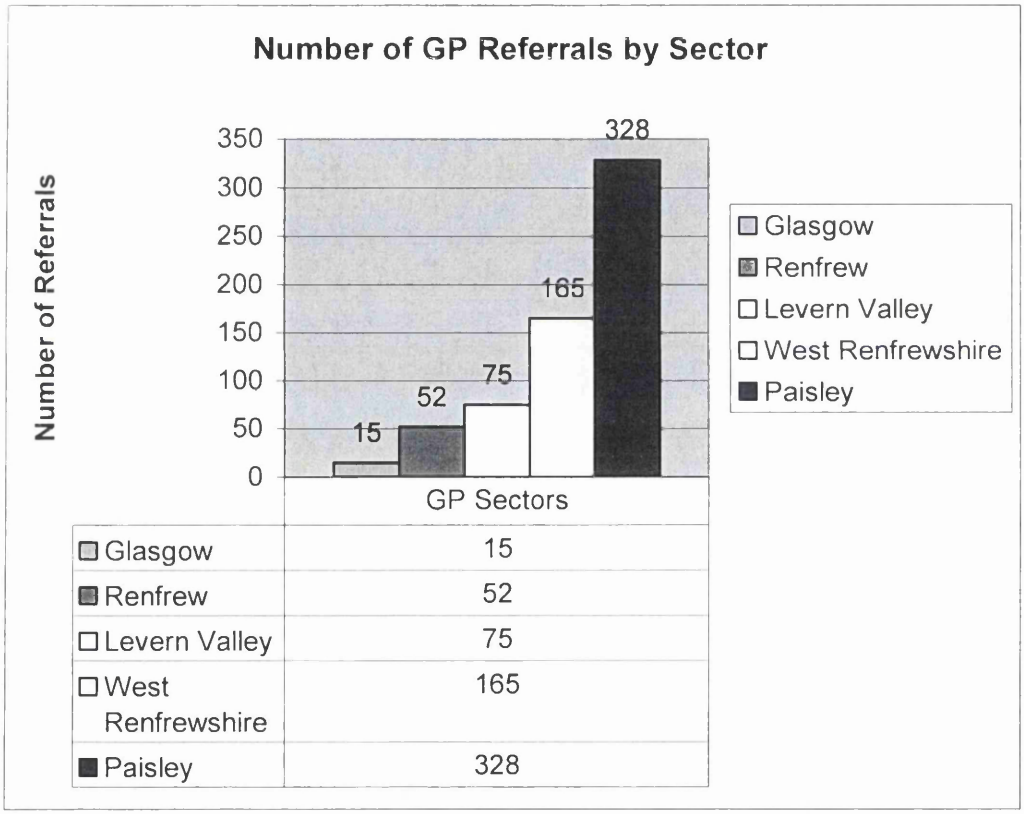


Figure 3: Scattergram of number of GPs and associated referrals

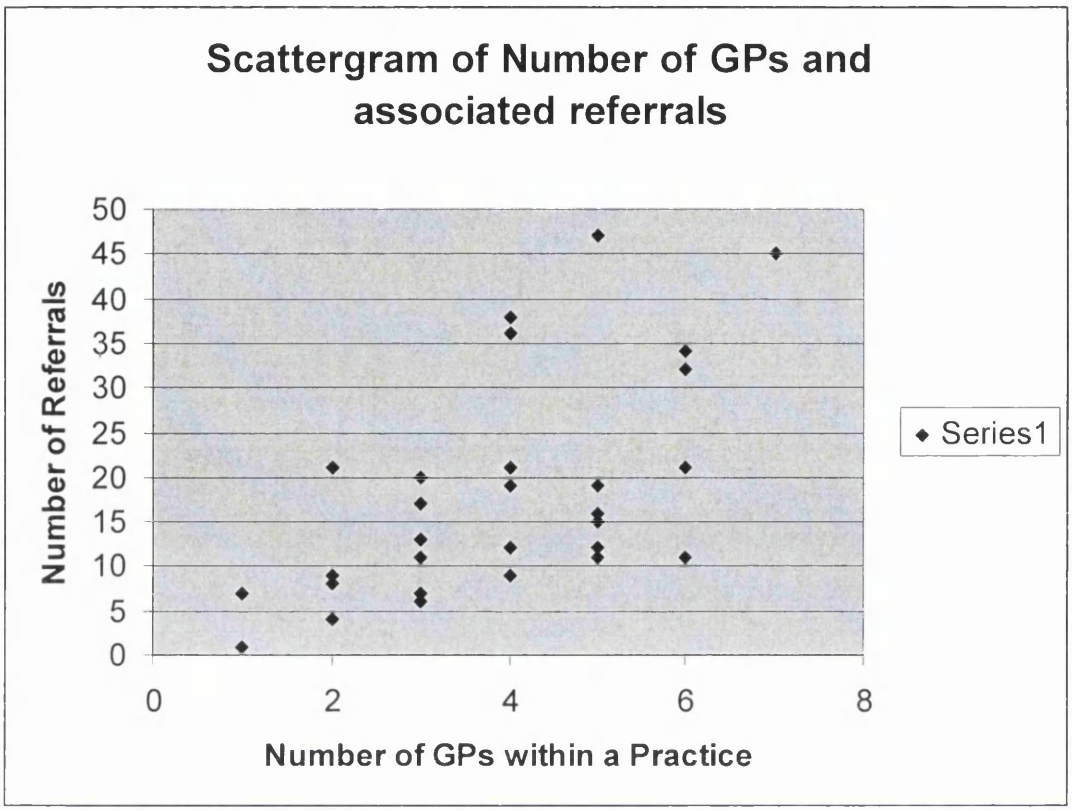


Table 3: Number of GP soon and urgent referrals

GP Referrals	Time 1	Time 2	Time 3	Total
Priority				
Soon	39	18	16	73
Urgent	9	4	3	16
Total	48	22	19	89

Figure 4: Graph of Number of Referrals by Age and Priority

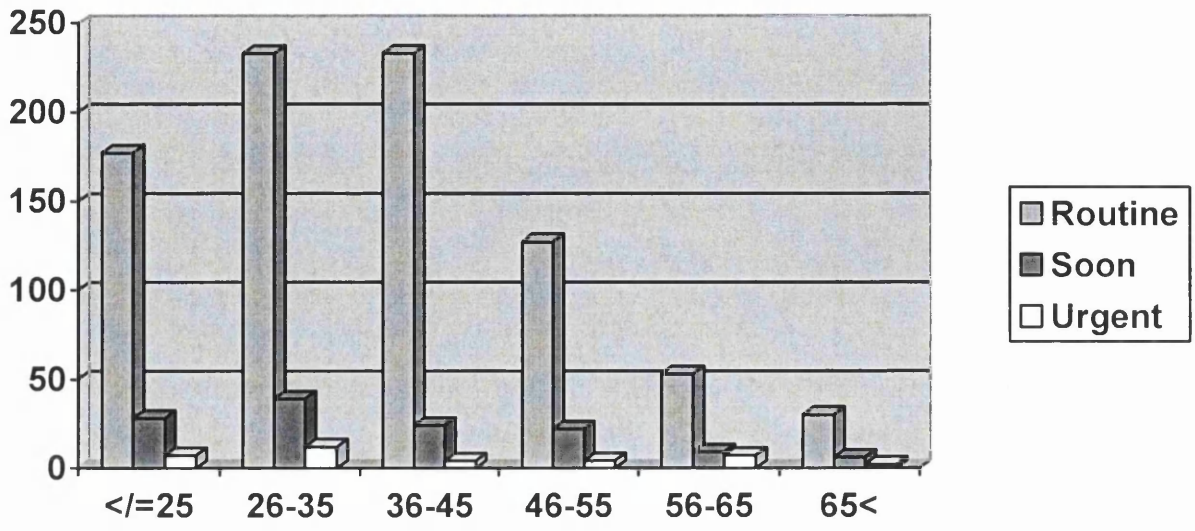
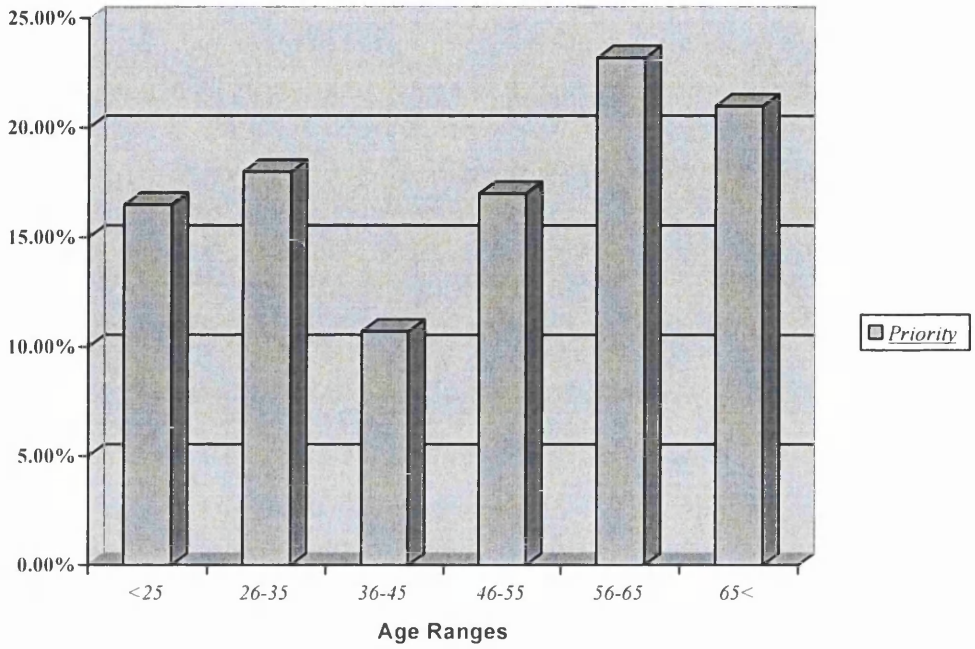


Table 4: Number of soon and urgent referrals in each age band

Priority	</= 25 years	26-35yrs	36-45yrs	46-55yrs	56-65yrs	65yrs<	Total
Soon	28	39	24	22	9	6	**128**
Urgent	7	12	4	4	7	2	**36**
Total	**35**	**51**	**28**	**26**	**16**	**8**	**164**

Figure 5: Graph of percentage of priority referrals within each age range



Number of referrals from each GP practice within divisional area sectors:

N = Number of GPs within the practice.

Levern Valley:

Practice	Time 1	Time 2	Time 3	Total
1. (N=2)	6	2	1	9
2. (N=6)	2	5	4	11
3. (N=2)	4	5	4	13
4. (N=6)	17	14	11	42

Total 75 referrals, 16 GPs

Paisley:

Practice	Time 1	Time 2	Time 3	Total
1. (N=2)	0	1	3	4
2. (N=2)	2	3	4	9
3. (N=5)	5	5	6	16
4. (N=5)	3	7	6	16
5. (N=4)	9	3	7	19
6. (N=3)	6	4	10	20
7. (N=6)	4	8	9	21
8. (N=2)	12	3	6	21
9. (N=6)	9	12	14	35
10. (N=4)	19	7	10	36
11. (N=4)	14	11	14	39
12. (N=7)	12	16	17	45
13. (N=5)	16	14	17	47

Total 328 referrals, 55 GPs

Renfrew:

Practice	Time 1	Time 2	Time 3	Total
1. (N=5)	7	3	5	15
2. (N=3)	7	4	6	17
3. (N=3)	7	4	9	20

Total 52 referrals, 11 GPs

West Renfrewshire:

Practice	Time 1	Time 2	Time 3	Total
1. (N=1)	0	0	1	1
2. (N=4)	0	1	0	1
3. (N=5)	0	1	0	1
4. (N=2)	0	0	1	1
5. (N=2)	1	1	1	3
6. (N=2)	2	2	1	5
7. (N=3)	0	3	3	6
8. (N=1)	2	4	1	7
9. (N=4)	3	3	3	9
10. (N=5)	3	3	5	11
11. (N=3)	4	3	4	11
12. (N=3)	3	2	6	11
13. (N=5)	5	5	2	12
14. (N=4)	4	4	4	12
15. (N=3)	6	2	5	13
16. (N=5)	7	7	5	19
17. (N=4)	3	9	9	21
18. (N=4)	9	6	6	21

Total 165 referrals, 47 GPs

Chapter 2: Systematic Review

The pathophysiological correlates of multiple sclerosis related cognitive impairment: A systematic review of magnetic resonance imaging findings.

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(See Appendix 2.1 for contributor's notes)

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Abstract

Magnetic resonance imaging is a powerful technique which allows in vivo visualisation of brain structures. This technique has been frequently used in research examining the association between pathological processes and cognitive impairment in multiple sclerosis. This review systematically examined the literature over the last decade that investigated the association between magnetic resonance imaging findings and cognitive impairment in multiple sclerosis.

Results from the review suggest that damage to the brain in multiple sclerosis occurs: early in the disease process, is diffuse, and involves the development of white matter lesions, regional atrophy, and global atrophy of cortical and subcortical areas. This pathology is associated with multiple domain cognitive impairment including attention, working memory, and executive processes.

INTRODUCTION

Research investigating brain abnormalities in vivo (both structural and functional) and their relationship with cognition in multiple sclerosis is a major field of contemporary research, utilising the potential of modern imaging technology in revealing the structure and function of the living brain. The major techniques currently used are magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), and positron emission tomography (PET). The scope of this systematic review will be to examine how structural changes revealed by MRI are related to cognitive performance in people with multiple sclerosis (MS).

Multiple sclerosis is the most common neurological disease affecting young and middle aged adults and involves a process of chronic autoimmune attack on the central nervous system that leads to inflammation and destruction of myelin sheaths surrounding neuronal axons (Arnett, 2003). This destruction eventually leads to demyelination and subsequent axonal damage and loss. Characteristic changes in areas of the multiple sclerosis brain are lesions in the subcortical white matter fibres, particularly in the periventricular areas, corpus callosum, and infratentorial areas (Filippi and Rocca, 2007). These lesions represent areas of various pathology in the MS brain including inflammation and demyelination, and chronic axonal loss. Long term axonal and myelin loss can contribute, along with other tissue loss, such as grey matter, to atrophy within the MS brain (de Stefano, Battaglini, & Smith, 2007).

Cognitive impairment is a well recognised and now accepted major symptom of multiple sclerosis with prevalence rates estimated to be anywhere between 45 – 65%, (Rao, 1995). However, it is only in the last few decades that this has become widely accepted and investigated (Bobholz and Rao, 2003). Due to predominately subcortical white matter aetiology in the MS brain, the cognitive domains or processes most affected are attention, speed of processing, and memory (DeSousa, Albert, & Kalman, 2002). More cortical subserved functions such as language ability are generally preserved with findings suggesting that widespread damage to white matter leads to a functional disconnection between different cortical areas and deep grey matter structures. Fibre damage can also lead to a slowing in neuronal communication affecting the speed of cognitive processes. Due to the somewhat unpredictable and quasi-random distribution of lesions in the MS brain, presentation and progression of cognitive deficits vary enormously between sufferers (Gainotti, 2006). The anatomical distribution of inter-individual MS pathology with respect to functionally eloquent areas and networks determines the clinical phenotype (Guttmann, Meier, & Holland, 2006).

During the last 10 years MRI has been increasingly utilized in the study of MS and "the overall landscape has dramatically improved compared to that of the mid-1990s" (Filippi et al., 2007). The aetiology and relationship between MS brain changes and cognitive impairment have been of great interest in the last decade with many researchers seeking to establish a link between MRI detectable abnormalities and the association with physical and cognitive disability (Rovaris, Comi, & Filippi, 2006).

Neuroimaging and Application in MS

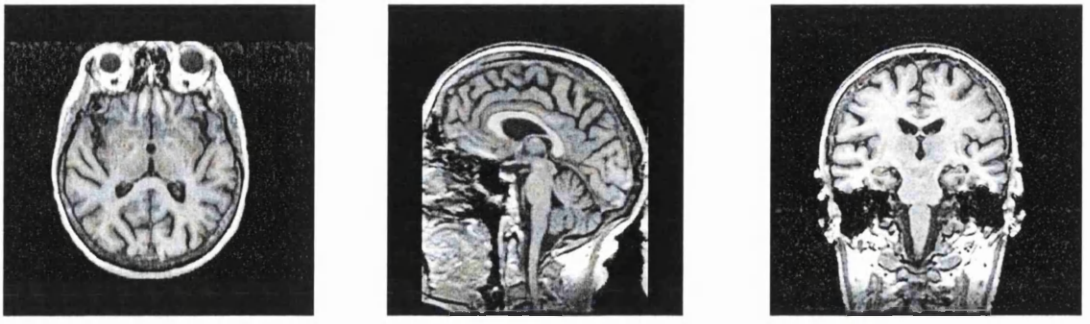
Magnetic resonance imaging (MRI) is one of the most important modern day brain imaging tools and offers high resolution structural imaging of the brain, displaying considerable contrast between the primary tissues of the brain: grey matter, white matter, and cerebrospinal fluid (CSF). MRI is based on the magnetic properties of hydrogen ions, which are abundant within water in the brain tissue. The hydrogen atoms have protons with a dipolar magnetic field that have an angular momentum analogous to a spinning top or the rotation of the planet earth spinning on its axis and the spins of the protons within the body are randomly aligned under normal conditions (Berger, 2002). However, when the body is placed under a strong magnetic field, as in an MRI scanner, the protons become aligned along the axis of the MRI magnet.

The movement of the protons around the axis of the magnetic field is called precession and the frequency with which they precess is known as their resonance frequency. When a radio frequency (RF) energy pulse is applied at the same resonant frequency of the protons, excitation occurs and the protons are disturbed away from the alignment of the external magnetic field to the transverse plane. When the RF pulse is then switched off two simultaneous processes occur: T1 relaxation and T2 decay. These processes involve the realignment of the protons to the external magnetic field with energy released to local tissue and a decay of the coherent precession or spin. From these two processes the protons emit a radiofrequency signal, which is the MRI signal, and this is detected by a receiver coil around the patient's head.

T1 relaxation and T2 decay are affected by the local tissue environment and can therefore be used to differentiate between the various compartments of the brain (Diwadker, & Keshaven, 2002). By altering the echo time (the time between the first RF pulse and subsequent MR signal), differences in T1 or T2 components can be emphasised, leading to different tissue contrasts. A T1 weighted image will give maximum contrast between tissues with different T1 types, therefore white matter with a short T1 appears bright, grey matter darker, and CSF darkest, in an MRI scan. A T2 weighted image will emphasise differences in tissues with different T2 times, leading to CSF being brightest, followed by grey matter, and then white matter. Further, a proton density (PD) weighted image can be performed in which grey matter appears brighter than CSF due to the greater density of protons found in grey matter. Using a gradient coil the MR signal can be localised, producing images of slices of specific brain regions required. This allows contiguous slices of the brain in a choice of image planes, either coronal (vertical), sagittal (side), or axial (horizontal) -Figure 1.

Figure 1: Axial, Sagittal, and Coronal sections of brain MRI scans (T1):

(Images courtesy of Johnson & Becker, 1995-1999)



(The superior resolution obtained from MRI clearly differentiates grey and white matter, CSF, and allows assessment of cortical and subcortical structures, which is of great interest in multiple sclerosis).

Current technology allows thin slices of the brain to be obtained which contain voxels, or volume elements of brain tissue as small a $1mm^3$. The benefit of such small voxel elements reduces partial volume effects in which the tissue may be heterogeneous, comprising different types of tissue. Thinner slices ensure greater homogeneity in tissue composition, as fewer voxels will contain a mixture of tissue types. The strength of the scanner used in MRI research in MS is important and field strength for a conventional machine is generally accepted as being 1.5 Tesla to allow detection of small MS lesions; however higher field scanners do invariably detect a higher numbers of lesions (Filippi et al., 2007).

In multiple sclerosis conventional T2 weighted lesions appear hyperintense or very bright against the non-diseased tissue and are the most readily visible MS lesions reflecting different pathologies of various stages including inflammation, oedema, and demylenation. This imaging method can be used to measure the total visible lesion volume. In a conventional T1 weighted scan, MS lesions appear hypointense and within the white matter areas these are known as "black holes". These types of imaging findings are thought to reflect more destructive pathology and axonal loss (Rovaris, Comi, & Filippi, 2006).

The assessment procedures or morphometric (shape) analysis of the MRI scans allow deductions to be made on the various brain structures and lobes. Region of interest (ROI) analysis assesses morphometric abnormalities through detailed parcellation of the structure(s) under investigation allowing measurements to be taken and

comparisons made with healthy, matched controls (Goldberg-Zimring & Warfield, 2006). Thus brain atrophy is used as an index to monitor pathologic evolution of MS activity and several studies have shown that brain volume is significantly reduced in patients and that cognitive impairment in MS may be related to decreasing brain volume rather than just increasing lesion load (De Stefano, Battaglini, & Smith, 2007). Basic segmentation or parcellation techniques of brain structures involved manual tracing of a selected region on the MRI image or semiautomated and automated techniques. These techniques are open to rater bias and are time consuming requiring a high level of interrater reliability. Further more advanced and sophisticated techniques have emerged that allows more detailed analysis and these include: voxel-based morphometry (VBM), high dimensional brain mapping.

Voxel- based morphometry allows the assessment of morphometric features that may be more difficult or too subtle to analyse through conventional ROI techniques and gives a comprehensive local, voxel-based assessment of brain anatomy (Guttman, Meier, & Holland, 2006). Subjects' data are transformed to the same stereotactic space in the spatial normalisation process, and then the normalised image is partitioned into the three compartments of the brain, grey matter, white matter, and CSF. The grey matter segments are then smoothed and statistical analysis of the smoothed grey images are performed to investigate voxel-based differences. High dimensional brain mapping involves mapping a patient's brain or an average of a group of patients' brains onto a template brain and assessing changes in this transformation. A variability map of the transformations can be produced which indicates the areas of difference between the patients and the template brain. From

this, differences in brain morphometry can be examined and structural differences highlighted.

More contemporary non-conventional imaging analysis techniques such as Magnetisation Transfer Imaging and Diffusion Tensor Imaging allow assessment of tissue damage in what is known as Normal Appearing White and Grey Matter (NAWM, NAGM). Microscopic areas of damage are not readily detectable on T1 or T2 weighted images and these techniques can quantify more fully the extent of MS 'occult' pathology in the brain (Rovaris et al, 2006). The magnetization transfer imaging provides a ratio with which to determine the integrity of grey and white matter tissue in normal appearing brain tissue (NABT) and has highlighted the global central nervous system involvement in MS pathology (Filippi & Agosta, 2007).

Diffusion tensor imaging is a technique that allows assessment of the integrity of white matter tracts in the brain. This non-conventional image analysis is of great interest in multiple sclerosis as white matter plaques and subsequent disconnectivity between brain regions has been reported as being significant in multiple sclerosis related cognitive deficits (Miller et al., 1998; Goldberg-Zimring et al., Warfield 2006). DTI is based on the impeded movement of water within axonal bundles due to myelin sheaths which leads to water diffusion parallel to the fibres: anisotropic diffusion. Neuropathological process, as in multiple sclerosis, that lead to microstructural changes in white matter and reduced axonal integrity are thought to interfere with normal anisotropy. MRI pulse sequences allow the assessment of white matter tracts and can show directionality and abnormal connectivity in white matter (Ge, 2006).

Assessment of Cognitive Dysfunction in MS

The assessment of the cognitive dysfunction in MS has been evaluated with research highlighting optimal tests that should be used with this group to assess any potential cognitive impairment (Sartori & Edan, 2006). Recommendations have included test batteries with the following characteristics:

1) Tests independent of motor coordination and visuosopatial ability.
2) Focus on attention, working memory, and speed of processing.
3) Brief administration to minimise confound of fatigue.

Sartori et al. (2006) recommend a brief 30-minute test battery that includes the Paced Auditory Serial Addition Test (PASAT), new learning with the California Verbal Learning Test, and digit span backwards. Importantly, the authors recognise the confounding factor of depression impacting on cognitive test results.

The PASAT has remained as one of the most common neuropsychological test measures used in MS clinical evaluation and research studies and is a core measure of the Multiple Sclerosis Functional Composite. Deficits on the PASAT are one of the most robust findings in the neuropsychology of MS (Hoffmann, Tittgemeyer, & von Cramon, 2007).

The Brief Repeatable Battery of Neuropsychological Tests (BRBNT) (Rao, 1990) is a well-established and frequently referenced assessment battery of cognitive change in MS (Gainotti, 2006).

This compound of tests includes:

PASAT	*Measure of Attention*
Symbol Digit Modalities Test	*Processing Speed*
Selective Reminding Test	*Verbal Memory*
10/36 Spatial Recall Test	*Visuospatial Learning*
Word List Generation	*Verbal Fluency Task*

These tests were decided upon by administering a comprehensive neuropsychological test battery of 31 test indexes to 100 patients with MS and 100 matched healthy controls and selecting the tests on which the MS group were most impaired. Rao (1990) found that the final test selection demonstrated a sensitivity value of 71% and a specificity value of 94% in discriminating between cognitively intact and cognitively impaired patients with MS.

SYSTEMATIC REVIEW AIMS

This systematic review examines the existing literature base on the application of magnetic resonance functioning to cognitive performance in multiple sclerosis over the last decade and investigates the fundamental question of what are the pathophysiological correlates of multiple sclerosis related cognitive dysfunction? To the best of our knowledge there are no published systematic reviews or meta-analyses on this topic.

OBJECTIVES

The principal objectives are to examine the association between MRI revealed brain pathology and cognitive deficits in multiple sclerosis looking specifically at correlations between cognitive performance on neuropsychological tests and related areas of brain damage and lesion load in multiple sclerosis groups. Due to the large number and variability of psychometrics used with this group, particular focus will be given to a measure of attention, specifically the Paced Auditory Serial Addition Test which is part of the validated Multiple Sclerosis Functional Composite (MSFC) used as an outcome measure in clinical trials (DeSousa et al., 2002) and two highly recognised expert panel guidelines on consensus approaches to cognitive assessment in MS: Minimal Assessment of Cognitive Functioning in MS (Benedict et al., 2002) and the Brief Repeatable Battery (Rao, 1990). Of interest is whether there are consistent pathophysiological findings in the literature that are related to attentional decline and can MRI findings elucidate our understanding of MS-related cognitive decline?

Within the review discussion will also focus on the particular strengths and limitations of conventional and non-conventional MRI protocols in relation to the question of the association between pathology and cognitive impairment. The review will propose a model of multiple sclerosis cognitive decline and offer recommendations into future directions of study involving magnetic resonance imaging and its application in studying cognitive deficits in this disorder.

METHOD

A systematic methodological approach was adopted in selecting published peer reviewed journal articles.

Search strategy

A systematic search strategy to find eligible studies was carried out using the following computerised Databases: Ovid Medline ®, CDSR, ACP Journal Club, DARE, CCTR, CINAHL, EMBASE, Science Direct, and PsychINFO over a 10 year period from February 1997 to February 2007. To compliment the electronic search, article reference lists were scanned for eligible articles and a hand search of three journals that regularly take articles in this field was conducted: Journal of Neuroimaging, Journal of Neurological Sciences, and Multiple Sclerosis.

The search terms used were kept deliberately broad in order to secure access to the full body of literature as possible. The following terms were used during searching:

MULTIPLE	in "title" field
SCLEROSIS	in "title" field
MS	in "title" field
COGNITI$	in "title, abstract, keyword" field
MEMORY	in "title, abstract, keyword" field
ATTENTION	in "title, abstract, keyword" field
EXECUTIVE	in "title, abstract, keyword" field
MRI	in "title, abstract, keyword" field
MAGNETIC RESONANCE	in "title, abstract, keyword" field

These search terms were combined using the 'AND' function to focus on retrieving the relevant literature and the following numbers of articles were retrieved:

1) Multiple and sclerosis within title with MRI and cogniti$ as keywords found 166 articles.

2) Multiple and sclerosis within title with MRI and memory as keywords found 73 articles. After viewing the abstracts of the articles, 36 were selected as being relevant.

3) Multiple and sclerosis within title with MRI and attention as keywords found 64 articles. After viewing the abstracts of the articles, 31 were selected as being relevant.

4) Multiple and sclerosis within title with MRI and executive as keywords found 13 articles. After viewing the abstracts of the articles, 6 were selected as being relevant.

All article titles and abstracts were examined and duplicates removed to leave a final list of potential articles that could be subjected to the following inclusion criteria.

Inclusion criteria

1) Studies assessing the association between cognitive impairment and MRI findings in multiple sclerosis found in published peer-reviewed journals. Clinical single N case reports and dissertation abstracts were not included.
2) Studies from previous 10 years of literature due to advances in and standardisation in MRI applications in this field and recognition and greater understanding of multiple sclerosis related cognitive decline.
3) Original data articles only.
4) Assessed cognitive function using validated neuropsychological methods.
5) Used the PASAT as an attentional measure.
6) Scanner field strength given and no less than 1.5 Tesla which is the baseline power for adequate signal-to-noise ratio.

7) Published in English language.
8) Assessed for mood using a validated measure.
9) Adult participants between 20 and 65 years of age.
10) Clinically definite multiple sclerosis as defined by internationally recognised (Poser et al., 1983) or (McDonald et al., 2001) criteria.
11) Standard measures of lesion load and/or atrophy indices used and described: T1, T2, cortical and subcortical atrophy, DTI, and MTR.
12) Provided data in the form of correlation or regression statistics.

Using the aforementioned search strategy and inclusion criteria a total of 16 studies were selected for inclusion in this review. In table 1, a summarised description of the key variables of each article is given. It was envisaged that a meta-analysis would be considered as part of the review, however due to the variability in imaging protocols, participant characteristics, and psychometric examination it was felt that this approach would not be feasible as the confounding variance was too large. Instead a critical analysis of the field was chosen as a suitable approach.

Table 1: Description of included studies

hor and Year	MS Participants and sampling	Characteristics of sample	Scanner Strength	Neuropsychological tests	MRI measures	Main findings
edict et al 02)	35 clinic and community	14 RR 21 Prog	1.5T	PASAT Boston Naming Test JoL CVLT BVMT WCST	TLA 3VW Cortical Atrophy	Positive association between frontal cortical atrophy and cognitive dysfunction.
edict et al 04)	37 clinic	30 RR 7 SP	1.5T	PASAT SDMT CVLT-II BVMT-R Boston Naming Test JoL COWAT WCST	TLA 3VW BPF	Brain atrophy, especially central atrophy accounts for and predicts cognitive impairment.
ss et al 06)	33 clinic	27 RR 6 SP	1.5T	PASAT SDMT CVLT-II BVMT-R JoL COWAT	TLA T2 Hypointensity BPF	Subcortical grey matter damage in basal ganglia associated with cognitive impairment
np et al 99)	63 clinic	43 PP 20 TP	1.5T	Brief Repeatable Battery	T2 Lesion Load T1 Hypointensity Cerebral Volume	Moderate association found between cognitive dysfunction and all MRI variables.
oire et al 05)	58 community	58 RR	1.5T	Brief Repeatable Battery Go-no-go Stroop BNT Ruff figural fluency	TLA BPF Gd lesions MTR of NABT	Attention and processing speed deficits significantly associated with lesion load and NAWM MTR.

ards et al 01)	41 clinic	21 RR 20 SP	1.5T	WAIS-R subtests WMS-III subtests PASAT FAS WCST Butter's 5 question task	GM volume WM volume CC volume Total cerebral volume	Significant correlations with WM volume and CC volume and cognitive. tests. No significant correlation with GM volume and tests.
ng et al 98)	13 clinic	4 RR 9 SP	1.5T	PASAT Stroop SDMT Digits forwards Story recall Spatial span	Gd lesions	Some improvement in tests scores in patient group where lesions had decreased after relapse.
ebrant et al 96)	45 clinic	45 RR	1.5T	WAIS subtests PASAT CVLT TAP	BPF VF	Main finding was correlation Of VF with memory performance.
ol et al 97)	44 clinic	14 RR 12 SP 13 CP 5 stable	1.5T	Brief Repeatable Battery	TL volume Brain volume	A 1 year follow up study. Worsening MRI lesion burden correlated with cognitive decline.
atelli et al 94)	39 hospital clinic	39 RR	1.5T	PASAT Stroop RPM	TLA TL frontal lobes Brain volume BPF Regional BPF	Brain atrophy and regional brain atrophy showed the best association with cognitive dysfunction.
gen et al 96)	19 clinic	19 RR	1.5T	PASAT TAP Digits forward/backwards Memo test	Brain atrophy	Performance on PASAT correlated with global and frontal grey matter volume. Atrophy linked with cognitive deficts.

Rovaris et al (1998)	30 clinic	10 RR 15SP 5PP	1.5T	PASAT SRT 10/36 Spatial recall Corsi Span Test WCST Stroop RPM Verbal Fluency	TLA FLA MTR	Total lesion area higher in patients with neuropsychological impairment and significant correlation with regional lesions and deficits.
Rovaris et al (2002)	34 clinic	34 RR	1.5T	PASAT SDMT Stroop SRT Verbal Fluency WCST WAIS (vocabularly) 10/36 Spatial recall	TLA Brain Volume Diffusion Tensor	Moderate correlations found between Subtest performance and lesion load and NABT.
Sperling et al (2001)	28 community	15RR 10CP	1.5T	Brief Repeatable Battery	TLA Regional lesion volume	Greatest proportion of lesions in frontal areas at all time points (4 year follow up WM lesions infrontal and parietal areas associated with cognitive deficits.
Zivadinov et al (2001)	53 clinic	53 RR	1.5T	PASAT Stroop Verbal fluency Digits forwards and bac RPM	TLA BPF	2 year follow up study found that cognitively impaired patients developed greater BPF atrophy.
Zivadinov et al (2001)	63 clinic	63 RR	1.5T	PASAT Stroop Verbal fluency Digits forwards and back RPM	TLA MTR BPF	In cognitively impaired patients the BPF and average NABT MTR were significantly lower.

Study Quality Rating

Due to the types of studies included in this review being non-randomised control correlational designs there are no predesigned methodological quality checklists available to use such as PEDro Scale (Maher et al, 2003) for cognitive rehabilitation studies. Instead the author designed a quality rating scale based on general recommendations from (SIGN 50) with regards assessing study quality. Each article was first rated to assess the methodological quality of each study in terms of:

- Clarity of hypotheses detailed
- Power calculation used
- Inclusion/Exclusion criteria specified
- Homogeneity of sample
- Quality of psychometrics used
- Controlled for participants with depression
- Control group used
- Experienced or supervised administrator of the neuropsychometrics
- Use of premorbid estimate of IQ
- Cognitive assessor blind to MRI findings
- Radiological rater blind to clinical and cognitive status.
- Scan acquisition and psychometrics performed within same time frame
- Appropriate statistics used

The scoring involved Yes = 1, No =0, Not Stated = 0 for all 13 criterion and quality rating for each article is provided in Table 2. Each paper was rated on the basis of these factors and a categorical rating of "excellent: >/=75%", "good: 50% - 74%", "adequate: 25% - 49%" or "inadequate <25%" was allocated to each paper based on the points awarded. From this there were no papers rated as inadequate, one rated as adequate, ten papers were rated as "good" and five papers were rated as "excellent" – see Table 2.

Reliability of the quality rating scale was checked by a second rater taking a random sample of five of the review articles and rating them according to the quality checklist. Any points of difference were discussed and resolved with full agreement over the final points allocated to each of the five articles.

Table 2 – Details of the quality rating for each study

Study	*Hypothesis Described*	*Power calculation*	*Inclusion/exclusion described*	*Same MS type*	*Validated psychometrics*	*Assessed for depression*	*Control group*	*Premorbid IQ assessed*
Benedict et al, 2002	Yes	No	Yes	No	Yes	Yes	No	Yes
Benedict et al, 2004	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Brass et al, 2006	Yes	No	Yes	No	Yes	Yes	Yes	No
Camp et al, 1999	Yes	No	No	No	Yes	Yes	Yes	Yes
Deloire et al, 2005	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Edwards et al, 2001	No	No	Yes	No	Yes	Yes	Yes	Yes
Foong et al, 1998	Yes	No	No	No	Yes	Yes	Yes	Yes
Hildebrandt et al, 2006	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Hohol et al, 1997	No	No	Yes	No	Yes	No	No	No
Locatelli et al, 2004	Yes	No	No	Yes	Yes	No	No	No
Morgen et al, 2006	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Rovaris et al, 1998	Yes	No	Yes	No	Yes	No	No	No
Rovaris et al, 2002	Yes	No	Yes	Yes	Yes	No	Yes	No
Sperling et al, 2001	Yes	No	Yes	No	Yes	Yes	Yes	No
Zivadinov et al, 2001	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Zivadinov et al, 2001	Yes	No	Yes	Yes	Yes	Yes	No	No

Study	*Cognitive assessor blind to MRI findings*	*Radiologist blind to cognitive results*	*Psychometrics and scan completed at same time*	*Appropriate statistical analysis*	*Statistics reported*	*Total Points Awarded*
Benedict et al, 2002	Not stated	Yes	No	Yes	Yes	**8 (61%)**
Benedict et al, 2004	Yes	Yes	Not stated	Yes	Yes	**10 (77%)**
Brass et al, 2006	Not stated	Yes	Not stated	Yes	Yes	**8 (61%)**
Camp et al, 1999	Not stated	Not stated	Not stated	Yes	Yes	**7 (54%)**
Deloire et al, 2005	Not stated	Yes	Yes	Yes	Yes	**10 (77%)**
Edwards et al, 2001	Not stated	Yes	Yes	Yes	Yes	**9 (69%)**
Foong et al, 1998	Not stated	Not stated	Yes	Yes	Yes	**8 (61%)**
Hildebrandt et al, 2006	Yes	Not stated	Not stated	Yes	Yes	**9 (69%)**
Hohol et al, 1997	No stated	Not stated	No	Yes	Yes	**4 (30%)**
Locatelli et al, 2004	Not stated	Yes	Yes	Yes	Yes	**7 (54%)**
Morgen et al, 2006	Not stated	Yes	Not stated	Yes	Yes	**10 (77%)**
Rovaris et al, 1998	Not stated	Yes	Yes	Yes	Yes	**7 (54%)**
Rovaris et al, 2002	Yes	Yes	Yes	Yes	Yes	**10 (77%)**
Sperling et al, 2001	Not stated	Yes	Not stated	Yes	Yes	**8 (61%)**
Zivadinov et al, 2001	Not stated	Yes	Yes	Yes	Yes	**10 (77%)**
Zivadinov et al, 2001	Not stated	Yes	Yes	Yes	Yes	**9 (69%)**

Review Results

Benedict et al. (2002) sought to determine the association between total lesion area, 3rd ventricular width, and region specific ratings of cortical atrophy and neuropsychological impairment. Thirty five clinic and community based patients were recruited for this study and administered a battery of cognitive domain specific tests examining language, visuospatial, memory, attention, speed of processing and executive functioning.

The general MRI measures looking at total lesion area accounted for more variance in all cognitive measures apart from the PASAT which was correlated with 3rd ventricular width. In a second stage analysis examining the prediction of neuropsychological impairment from cortical atrophy after controlling for total lesion area and 3rd ventricular width found that failures on tests of new learning, divided attention, and conceptual reasoning correlated strongly with superior frontal cortex atrophy. The main finding is an association between cognitive dysfunction and cortical atrophy in the frontal areas.

Benedict et al. (2004) looked at whether lesion burden or brain atrophy account for most of the variance in MS related cognitive decline. Thirty seven MS patients (clinic based) and 27 healthy controls participated in the study and underwent a battery of neuropsychological tests examining multiple cognitive domains and underwent MRI with four imaging analysis variables considered: T1 hypointense lesion volume, FLAIR lesion volume, bicaudate ration, and 3rd ventricular width and a cortical atrophy measure using brain parenchymal fraction. Patients performed poorly

compared to controls across a range of tests involving memory, attention, and speed of processing tasks. The authors found that 3rd ventricular width (3VW) and brain parenchymal fraction (BPF) accounted for more variance in MS cognitive performance than the total lesion burden. This finding may be explained by the anatomical significance of the thalamus which is close to the 3rd ventricular area and has widespread cortical and subcortical reciprocal connections. When 3WV was excluded from analysis, brain parenchymal fraction accounted for most variance indicating that central and whole brain atrophy account for more variance in MS cognition than lesion burden.

Brass et al. (2006) investigated lesion load in the subcortical grey matter by looking at the relationship between T2 grey matter hypointensity and the relationship with cognitive impairment after adjusting for the effects of whole brain measures of brain atrophy and total lesion load. Thirty three patients with relapsing-remitting (RR) and secondary progressive (SP) MS were recruited and 14 healthy controls. Imaging assessment calculated total T2 lesion load, brain atrophy (BPF), and T2 hypointense lesions in grey matter brain regions. Neuropsychological assessment involved a range of standardised tests that were administered to assess all cognitive domains and yield a final neuropsychological composite score. The tests included the CVLT, BVMT-R, PASAT, SDMT, JLO, COWAT. The main findings were that T2 hypointensity of the globus pallidus showed the strongest MRI correlation with neuropsychological composite score (NCS). Therefore, subcortical grey matter damage and cognitive impairment in MS patients is strongly associated. Further, BPF was another variable that was related to the NCS and has been shown in previous studies to correlate with

neuropsychological dysfunction. The authors suggest a clinical role for the T2 hypointensity as a biological marker of MS tissue damage.

Camp et al. (1999) aimed to investigate the relationship of MRI parameters and cognitive impairment in particular subtypes of MS: primary progressive and transistional progressive (TP). Sixty three patients were compared with healthy controls and were administered the Brief Repeatable Battery and a verbal and spatial reasoning test. MRI variables looked at included lesion load and cerebral atrophy measures. The main findings were that patients with PP and TP had cognitive deficits in the areas of memory, attention, fluency, and spatial reasoning when compared with healthy controls. No deficits in verbal reasoning were found. In the patient group 28.6% were cognitively impaired on a criteria of being more than 2 SDS on three or more tests. A cognitive impairment index was constructed and this correlated with the T2 lesion load ($r = 0.45$; $p = 0.01$), T1 hypointense lesion load ($r = 0.45$; $p = 0.01$), and cerebral volume ($r = -0.35$; $p = 0.01$). The authors conclude that in this subtype of patients, conventional MRI does not adequately explain the pathology and its effects.

Deloire et al. (2005) aimed to determine the relation between cognitive abnormalities and extent of cognitive abnormalities using conventional and non-conventional (MT) imaging in a population based sample of early RR MS patients. Fifty eight patients (with less than 6 months diagnosis) were matched with 44 control participants. Neuropsychological assessment was carried out on the same day as MRI acquisition and included Rao's Brief Repeatable Battery, a computerised version of a go-no-go task and Stroop test and the WAIS-R similarities test, Boston naming Test, and Ruff

Figural Fluency Test. Blinded image analysis took place of T1, FLAIR, and MT scans looking at lesion volume, atrophy measures, MTR measurements, and Gadolinium enhancing lesions. On neuropsychological measures, significant differences were found between the 44 matched patients and controls for all tests including attentional and information processing speed functions. Of the 44 matched RRMS patients, 45% scored below the 5^{th} percentile in two or more tests and 86% scored below the 5^{th} percentile in at least one test; only 13% of patients had no test under the 5^{th} percentile.

Lesion load was significantly correlated with attentional test scores: SDMT correct answers ($p<0.0001$, $r = -0.51$) and PASAT 3s correct answers ($p<0.05$, $r = -0.34$. No correlation found on memory tasks, inhibition tasks, or similarities. No correlations were found between Gadolinium enhanced lesions and cognitive scores. Atrophy (BPF and ventricular fraction) were not correlated with cognitive scores.

MTR used to assess tissue damage outside visible lesions in the NAWM and NAGM found significant correlations with NAWM and PASAT 3s. NAGM was correlated with SDMT scores. The neurobiological correlates of the cognitive dysfunction (attention and information processing speed) were lesion load and mean NAWM MTR which reflects the extent of the visible lesions and the damage within NAWM outside lesions.

Edwards, Liu, & Blumhardt (2001) looked at relationship between supratentorial white matter volumes and neuropsychological performance in 41 patients (RRMS and SPMS) recruited from an MS clinical database. MRI scans were done within 72 hours

of neuropsychological testing. Twelve controls matched for age and sex were used for neuropsychological assessment. MRI image analysis was performed by a neurologist blinded to clinical and neuropsychological data. Volumes were calculated of: total GM, total WM, combined ventricular volume, and total cerebral hemisphere volume. The corpus callosum was also measured. The neuropsychological battery comprised NART, WAIS-R subtests, WMS-R subtests, PASAT, FAS, WCST, Butter's test of abstract reasoning. The scores on these tests were combined to provide a global Cognitive Index Score (CIS) with a minimal and maximal cognitive deficit being (0) and (44) respectively. The global CIS was significantly correlated with white matter volume, total cerebral hemisphere volume, and corpus callosal area but not with grey matter volume or ventricular volume. White matter volume was also correlated with many individual cognitive tests but GM did not with any. With regards the PASAT performance it correlated strongly with the corpus callosum area. T2 lesion load was only correlated with the PASAT.

Foong et al. (1998) recruited 13 patients during clinical relapse to examine cognitive performance and the relationship with brain pathology under active MS attack. The MRI procedure involved gadolinium enhanced T1 scans that allow greater contrast of emerging lesions in the brain, especially during relapse. These scans were repeated at the beginning of the relapse and approximately 6 weeks later during remission. In addition, a neuropsychological test battery including the PASAT was administered to patients on both occasions. Patients performed significantly worse on the PASAT during the first testing session compared to the control group but made a considerable improvement on the PASAT score at the second testing session. The patients with relapsing remitting MS performed significantly better than the other patient subtypes.

In a subgroup of 6 patients that had a reduction in gadolinium lesion load during after the relapse, there was a significant correlation with improvement on attentional tests ($r = -0.99$, $p<0.01$ and $r = -.082$, $p<0.05$. These findings suggest that the reparation processes that brain initiates during a relapse can improve cognitive performance. Any deficits detected during relapse may be reversible as the active gadolinium enhanced lesions are not chronic at this time and may only reflect inflammation and not demyelination or axonal loss.

Hildebrandt et al. (2006) examined the impact of central and whole brain atrophy on neurocognitive performance in 45 relapsing remitting patients using a selection of multidomain subtests including the PASAT and a computerised attentional test, the TAP (Zimmermann and Fimm, 1992). An automated brain volumetric procedure was employed to examine the BPF (Brain Parenchymal Fraction), which is an index of whole brain atrophy, and VF (ventricular brain fraction), which is a regional measurement, related to subcortical midbrain areas. Interestingly, only VF correlated with cognitive variables in this patient group and the correlation was only significant with tests of memory performance. This finding may be due to the VF being anatomically close to limbic structures involved in memory. The lack of correlation with brain atrophy and the PASAT could be explained by the relatively mild disability in this patient group and that PASAT-BPF correlation is more likely if regional atrophy in the frontal lobe is examined.

Hohol et al. (1997) designed a longitudinal study to look at progression of disease burden and cognitive performance over 1 year in a sample of 44 mixed MS patients. The Brief Repeatable Battery was used on both testing occasions.

MRI scans using 3 dimensional automated volumetric analysis were also repeated and total lesion volume was calculated and a TLV slope for each patient was calculated over the year to estimate the amount of lesion change. Overall brain volume was also measured as an index of cortical atrophy. The mean cognitive performance did not decline over the year but 4 patients did perform worse at follow up and declined on the PASAT amongst others. Significant correlations between change in performance for the PASAT and MRI changes as assessed by the TLV slope was found for the entire group. Chronic progressive patients with consistent increases in the TLV slope over time demonstrated the worse performance on the PASAT.

Locatelli et al. (2004) examined whether normalised brain atrophy analysis correlated better than absolute brain atrophy measures with tests assessing cognitive functioning. Thirty nine relapsing remitting MS patients were administered the PASAT, Stroop, and Raven's Matrices. The PASAT was correlated with regional brain parenchymal fractions of the frontal lobes ($r=0.77$; $p<0.0001$, and whole brain atrophy ($r=0.60$;$p<0.0001$). This study used an automated segmentation analysis to look at normalised regional brain atrophy and concluded that normalised analysis of brain atrophy were better related to cognitive dysfunction with regional atrophy within the frontal lobes significantly associated with poorer PASAT performance.

Morgen et al. (2006) recruited 19 relapsing remitting patients in the early stages of the disease to examine association between brain volume and cognitive performance with the view that grey matter pathology is a major contributor to MS related cognitive impairment. MRI measurements included global and regional white matter and grey matter volumes and white matter lesion load.

Cognitive tests used were the Digits forward and backwards, the Memo test, the PASAT, and the TAP computerised attentional test (Zimmermann & Fimm1992). The main findings were that grey matter volume decrease in the patients correlated with impaired cognitive performance. Poorer performance on the PASAT was linked with widespread cortical volume decrease in the frontal and temporal cortices. The authors suggest that cortical neuronal damage may be a result of retrograde axonal damage from fibre connections with periventricular white matter lesions. Surprisingly, in this group there was no correlation between white matter volume and cognitive impairment.

Rovaris et al. (1998) used both conventional and nonconventional MRI imaging protocols to assess cognitive impairment and lesion correlations. The use of magnetisation transfer was hypothesised to more fully assess burden of pathology in the NAWM. Thirty clinic-based patients of mixed subtypes (RR, SP, PP) were administered an extensive neuropsychological test battery including the PASAT with total lesion load, frontal lobe white matter lesion load, and average magnetisation transfer ratio (MTR) in whole brain and frontal lobe calculated. Fifteen patients were found to have frontal lobe impairment and the mean frontal lesion load was significantly higher than in patients with unimpaired frontal lobe functions. No significant correlation was found with the PASAT performance and MRI findings. Further, the authors found that cognitively impaired patients had lower magnetisation transfer ratio implicating microscopic pathologic changes affecting the NAWM as well as macroscopic lesions.

Rovaris et al. (2002) used diffusion tensor imaging to investigate correlations between white matter integrity within and outside macroscopic MS lesions and neuropsychological performance in a group of mildly disabled relapsing remitting patients. An extensive battery of neuropsychological tests were administered including the PASAT and subsequently 9 patients were categorised as being cognitively impaired due to being more than 2 standard deviations below control mean in three or more tests. Twenty patients in the sample scored more than two standard deviations below the control mean for the PASAT. There was a trend for the cognitively impaired group to have more lesions than the unimpaired group but interestingly this did not reach statistical significance. The highest correlations – that were still only of moderate strength – were found for the semantic fluency test and symbol digit modalities test, but not the PASAT. There was no significant difference in diffusion tensor derived MRI metrics between the cognitively impaired group and unimpaired group, which was unexpected.

Sperling et al. (2001) undertook a 4-year follow up study to measure longitudinal cognitive performance and the relationship with evolving MRI brain changes in 28 community-based patients. Total lesion area and regional lesion volume were calculated at baseline, 1 year, and 4 year follow up. Manual delineation of cerebral hemispheres was conducted to yield 8 regions of interest: frontal, parietal, temporal and posterior in each hemisphere and automated analysis identified volumes of lesions within each region. The Brief Repeatable Battery (Rao, 1990) was administered at all corresponding time points. MS patients were impaired on all baseline neuropsychological measures, compared with controls, with the most significant difference found on the PASAT. At both 1 year and 4 year follow up there were no

significant changes in cognitive test scores for patients or significant increases in lesion volume. Cognitive performance was significantly correlated with specific regional and total lesion volumes at all test points. Performance on the PASAT was significantly correlated with frontal, parietal, and total lesion burden ($R = -0.55$ to -0.74; $p<0.001$). The authors suggest that the regional distribution of lesions in MS is not random and lesions show a predilection for frontal and parietal regions.

Zivadinov et al. (2001) used a longitudinal study to assess whether cognitive changes in MS were dependent on the progression of the lesion burden, reduction in brain parenchyma, or both. Fifty three relapsing remitting patients underwent serial MRI scans and an extensive neuropsychological test battery at two time points with all patients being categorised into one of three groups at follow up: cognitively improved patients, cognitively stable patients, and cognitively worsened patients. At follow up 28 patients were judged as cognitively impaired and 15 worsened. At follow up the patients showed a significant increase in lesion load and decrease in brain parenchymal volume. The cognitively worsened group showed a significantly higher loss of brain parenchyma and this was significantly related to changes in cognitive performance. There was a significant change in patients' PASAT scores over the two years and the authors suggest that in the early phase of relapsing remitting MS cognitive deterioration depends more on the development of brain parenchymal atrophy rather than extent of lesion burden.

Zivadinov et al. (2001) explored which conventional or nonconventional MRI marker correlated best with cognitive impairment in early relapsing remitting MS. Sixty three relapsing remitting patients were administered a battery of neuropsychological tests

including the PASAT and MRI total lesion area, magnetisation transfer ratio, and brain parenchymal fraction were calculated. Fifteen of the patients in this sample were judged to be cognitively impaired (based on deficits in two or more cognitive domains) and no significant differences were found between cognitively unimpaired and impaired patients on total lesion load and average lesion MTR. In the 15 cognitively impaired patients there was a significant difference in brain parenchymal fraction and average normal appearing brain tissue MTR compared to cognitively intact patients.

Discussion

There were consistent findings across papers that MS related damage to the brain leads to cognitive impairment. There were no gross differences between papers and conclusions were consistent regardless of study quality. The review findings suggest that the pathophysiological correlates of multiple sclerosis related cognitive dysfunction are multiple and diffuse with many cortical and subcortical regions of brain tissue contributing to cognitive impairment. Lesion load as detected by T1 and T2 imaging parameters correlates with cognitive performance on a wide range of psychometric tests. Further, global atrophy as found with the brain parenchymal fraction and local atrophy in the 3rd ventricular area, corpus callosum, and frontal cortex, are all related to cognitive impairment. Cognitive deficits correlate with brain lesion burden and brain atrophy (Amato, Zipoli, & Portaccio, 2006). However the number of MRI visible lesions on conventional imaging protocols does not fully account for the severity of the cognitive impairment (Rovaris et al., 2006). The application of non-conventional MRI protocols such as magnetisation transfer and diffusion tensor imaging has allowed assessment of normal appearing brain tissue and this has revealed that there are microscopic areas of damage outside of visible lesions which contribute to the cognitive decline.

Particular focus was given to brain pathology linked with performance on the PASAT and every study in the review used the PASAT as a cognitive measure as deficits on this test are one of the most robust findings in the neuropsychology of MS (Hoffmann et al., 2007).

Unsurprisingly there was no single type of pathology that was solely linked with impairment on this test with studies reporting correlations between: corpus callosum area, 3VW, total lesion load, non-visible lesions within NABT, frontal and parietal atrophy, and global atrophy, and test performance. It is likely that such a test is subserved by activation in multiple brain areas explaining why variable pathology affects performance on it.

These results are not unexpected and provide in vivo insight into the pathogenesis of cognitive disturbances in MS. The imaging literature has elucidated our understanding of the underlying pathology and its relationship with cognitive impairment and reveals quite clearly that the model of cognitive dysfunction is not due to one primary variable such as white matter lesions but a combination of many pathogenic variables affecting the global brain.

Cortical and subcortical atrophy along with disconnection of interneuronal networks within the cortex and white matter play a role in the cognitive decline. This breakdown leads to reduced processing speed in the brain which then affects attentional resources and memory. The ability of brain areas to 'talk' to different brain areas in close proximity and over longer distances becomes compromised leading to a failure to synchronous neural firing. It is clear that damage to the brain takes place early in the disease process and involves volume reduction too, either through cell loss or axonal degradation. The pattern of cognitive impairment is linked with the subtype of the disease. Relapsing remitting MS involves a process of axon attack and reparation and the cognitive impairment is less severe and follows a stepwise pattern.

In the progressive subtypes the cognitive impairment can follow a more steady and severe decline due to non remission of the disease process. Of note, there is a large amount of variability between individual patients and the individual pattern of brain damage dictates the cognitive outcome. For example, multiple lesions in the mid-brain limbic system will significantly impact on new learning while a preponderance of frontal subcortical lesions will affect working memory.

Looking beyond the science of imaging protocols and psychometrics, more fundamental issues within this field need addressed and considerable criticism can be levied towards the methodological issues endemic within this area. For example, few studies ensured a homogeneity of sample with different subtypes of MS with different disease durations often combined. Future studies should focus on the cognitive-pathology profile within definite subtypes of patients with clearly defined definitions of the different temporal stages of MS. For example, when does someone with MS stop being in the "early stages"?

The definition of cognitive impairment is not universally defined either with some authors taking the view that cognitive impairment is based on magnitude of the standard deviation on a certain number of tests. Reliable criteria should be established to determine when one patient with MS is cognitively impaired and another not. Perhaps this should always be based on the inclusion of an age and education matched healthy control group to compare test performance.

In all the studies, the statistical methods used to link cognitive dysfunction and structural changes are usually either a correlation or regression analysis with individual or summarized cognitive index scores being separately analysed with structural changes. Hoffmann et al., 2007 recommend multiple regression modeling techniques based on summarized cognitive scores to be performed in order to increase precision and reliability.

In assessing the cognitive impairment in this group it is recommended that a brief battery be used to avoid confounding effects of fatigue and should minimise tests with a significant motor or visuospatial component. It is recommended that test batteries focus on the use of the PASAT, which is test that has been repeatedly validated for use with this population and is sensitive to the cognitive changes that take place in MS (Achiron et al., 2005). In addition, Sartori et al., (2006) recommend the use of digit span backwards which further examines attention and working memory and a verbal learning test, the CVLT. Also, the SDMT has shown high rates of sensitivity (Parmenter, Weinstock-Guttman, & Garg, 2007) in multiple sclerosis. The timing of the cognitive assessment is crucial and should be outwith relapse episodes and corticosteroid therapy which both reduce cognitive performance (Foong et al., 1998; Oliveri et al., 1998). In addition, assessment of mood is vital due to the significant association found between mood disturbance and cognitive impairment (Bobholz et al., 2003).

Further studies should use more advanced measures in addition to conventional imaging protocols that measure lesion load. For example, DTI can provide information on axonal integrity and direction (Goldberg-Zimring et al., 2006), while MTI can provide information on the global extent of the pathology in the NABT

(Filippi et al., 2007). The combination of effective imaging protocols with the use of sensitive measures of cognition should increase understanding of the extent and nature of the correlation between imaging findings and cognitive dysfunction in multiple sclerosis.

Of interest, but beyond the scope of this review, it may have been revealing to look at functional imaging findings including PET, fMRI, and electrophysiological recordings using the ERP technique. Perhaps there may be an overlay between structural degradation and functional activation during task performance? Or in line with recent evidence, functional compensation during cognitive tasks may be linked to specific lesion sites in the MS brain? These important questions should be addressed and will further elucidate our understanding of the neuroanatomical correlates of MS related cognitive dysfunction.

This review is not without limitations, which may affect the synthesis and conclusions made in this research area. The inclusion criteria contained points which impacted on the number of studies included in the review. For example, this review accepted literature written in English from a 10-year period. The preliminary search identified a relatively large number of articles over several decades and these may have added to the review. However, due to increases over time in MRI technology and greater understanding of MS related cognitive decline it is highly unlikely that they would have changed the outcome of the review. Very few papers were excluded because they did not state the scanner strength or cognitive tests used but communication with the authors may have clarified this and led to inclusion of the study within the review. Again, it is unlikely that this would have altered the face of the results.

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Chapter 3: Major Research Project Proposal

Is there a central executive attentional deficit in Multiple Sclerosis? Evidence from single and divided attentional paradigms.

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Summary of Project

This study is concerned with exploring possible attention deficits in a neurological population, namely participants with a diagnosis of multiple sclerosis. Specifically, we are interested in whether participants in the early stages of multiple sclerosis, have deficits with single visual and auditory attention, and divided attention. Using computer based paradigms, attention abilities will be examined in unimodal visual and auditory conditions and bimodal visuo-auditory conditions. Results will be compared to a non-clinical, age and education matched control group. Results will be discussed within a cognitive theoretical framework, focusing on a 'central executive attention allocator'.

Introduction

Multiple sclerosis (MS) is a neurodegenerative inflammatory demyelinating condition of the central nervous system with a variable clinical course involving several disease subtypes. Multiple sclerosis means 'many scars' and disease progression follows four main subtypes, however the most common subtype is relapsing-remitting multiple sclerosis, characterised by acute attacks of neurological dysfunction, followed by partial or complete recovery (SNAP, 2000). In addition, prevalence rates are calculated at 144 cases per 100,000 of the population in the West of Scotland. The pathology and ensuing disability is linked with the process of axonal demyelination, remyelination, and axonal and synaptic degeneration (Orhun, Kantarci, Brian, Weinshenker, 2005). The accumulating lesion profile in the brain is diffuse, affecting central nervous functioning, motor systems, and multiple brain regions. The clinical manifestation of the disease varies considerably between sufferers and is related to lesion site and subsequent effects on function.

In addition to the physical problems experienced, cognitive impairment in MS is well documented and estimates of cognitive deterioration in patients range from 45 – 65%, (Rao, 1995). The nature and course of MS is heterogeneous and recognized cognitive deficits involve a range of domains including memory, attention, and speed of information processing (Zakzanis, 2000). Lezak, (2005) reports common circumscribed deficits in the cognitive domains of attention, memory, and executive function in relapsing-remitting patients. Spilich, Mubrin, and Janculjak (2002) state that changes in cognitive processes may appear long before the physical

manifestations of MS, suggesting that identifying patients earlier could be based on cognitive changes.

Even though the cognitive profile in MS is often heterogeneous, a consistent deficit found in multiple sclerosis is deficits of attention and the ability to attend to more than one thing at the same time, divided attention (Bobholz & Rao, 2003). In addition, an intact attentional system is vital for the efficient processing of other various cognitive systems, for example memory encoding. There is some suggestion that deficits in higher cognitive operations are actually secondary to primary attentional problems in MS. However the extant MS literature examining attentional dysfunction leaves unanswered questions as to the extent and nature of deficits (McCarthy, Beaumont, Thompson, Peacock, 2005).

When considering the concept of attention there are various theoretical cognitive models of attention and one of the most influential and frequently referenced theories is Baddeley's, (1986) working memory model. He proposed a structural model involving multiple interactive components including a central executive controller that regulates and distributes the limited available attentional resources that a system possesses, and visuospatial and phonological slave systems (Baddeley, 2003). The slave systems are responsible for storage of modality specific inputs and one of the principle roles of a central executive system would be to efficiently allocate and manage attentional resources when two or more tasks are being executed

simultaneously or when attention is divided between the visual and auditory slave systems (Baddeley, 1996).

Dual tasking or divided attention paradigms have been used extensively to study this fundamental property of an executive control system in various patient populations (Baddeley, Della Sala, Papagno, Spinnler, 1997). Dual tasking designs involve performing two different tasks on their own and then concurrently, and comparing performance levels on one or more of the tasks. For example, eastablished formats involve participants performing a verbal digit span task with a visual tracking task. In clinical populations, a dual task performance decrement is frequently observed and reported in the context of damage to an executive coordinator responsible for dividing and allocating attention; for example in Alzheimer's disease (Logie, Della Sala, Cocchini, Baddeley, 2004).

Further, Baddeley, Bucks, Wilcock, (2001) found that Alzheimer's disease patients have a specific difficulty with dual task performance, even when controlling for the general overall cognitive demand, suggesting that available attentional resources is not the problem, but how they are allocated is. Also, in a frontal lobe lesion patient group Baddeley et al, (1997) found that patients with dysexecutive syndrome showed impaired capacity for dual tasking.

In multiple sclerosis, evidence indicates that the the multifocal lesion profile may affect brain areas which form the working memory substrate, leading to working memory impairment in the early stages of the disease (Pelosi, Geesken, Holly, Hayward, Blumhardt, 1997).

D'Esposito, Onishi, Thompson, Robinson, Armstrong, and Grossman, (1996) investigated central executive functioning using dual tasking methodology comparing an MS group with a control group. In their study, the dual tasking paradigm involved performing a primary task concurrently with one of three secondary tasks. The primary task involved a line orientation judgement with the concurrent secondary tasks being finger tapping, alphabet recitation, and humming a melody. Results showed that the MS group performed less well during the more demanding dual task conditions (humming a melody and alphabet recitation) than the control group. The authors concluded that the dual task decrement found in the MS group, reflected an impaired central executive of working memory resulting in difficulty allocating sufficient attentional resources to support concurrent task execution.

Baddeley et al (1997) states that paradigms exploring the central executive's coordination properties should involve simultaneous operation of the phonological loop and visuospatial sketchpad. A criticism of De'Esposito et al, (1996) study is that their paradigms utilise tasks that recruit higher cognitive functions of language, memory, and musical ability, and fail to isolate the basic properties of the working memory model.

Paul, Beatty, Schneider, Blanco, and Hames (1998) investigated several aspects of automatic and controlled attentional processing in MS using tests of focused and divided attention. They used the Posner spatial attention task (Posner, Cohen, Rafal, 1982), which involves visual stimuli presented with valid and invalid spatial cues, as a test of automatic processing and found that the MS group performed as well as the control group. The Paced Auditory Serial Addition Task (PASAT) was used as a test of divided attention in this study and the MS group performed significantly worse than the controls. Whether the PASAT is truly a test of divided attention is worthy of thought as the nature of that task involves sustained attention over time with higher cognitive functions of calculation recruited. Often, the PASAT is used as an index of information processing speed and clearly, there is a large working memory involvement, but it is questionable whether this test fulfils the criteria that Baddeley, (1997) suggests for divided attention methodology.

Recently, McCarthy, Beaumont, Thompson, and Peacock, (2005) considered the profile of attentional dysfunction in MS using divided and sustained attention methodology across unimodal and bimodal visual and auditory trials. The authors developed two new measures of sustained and divided attention as part of their study and recognised that their approach to investigating divided attention was in contrast with conventional dual tasking methodologies where primary task decrement is measured during concurrent secondary task execution. In the divided attention task, targets were digits that were consecutive pairs either ascending or descending with a temporal delay between digit presentation in a trial. Participants were required to divide their attention between retention of the first digit and presentation of the next

digit. Thirty MS participants were compared with 30 controls across all six conditions (sustained vs divided task and auditory, visual, bimodal presentations). The results suggested that the MS group performed slower and less accurate than controls on both sustained and divided measures of attention. Of note, the MS group were disproportionately slower on the bimodal trials of the divided attention task, relative to unimodal trials. The authors concluded that their results were not related to motor slowing or information processing speed deficits, but linked with the task demands and the modality targetted. When the MS group were performing the divided attention task in visuo-auditory bimodal trials, their performance suffered most and this could be explained within Baddeley's, (2003) theoretical framework with a deficient central executive component, impaired in allocating attentional resources efficiently between visual and auditory modalities.

The general aspect of this present study is to further understand the nature of cognitive impairment in MS, and in particular to investigate further the attentional system in multiple sclerosis, in the early stages of the disease. Specifically, we are interested in the participant's ability to divide their attention during concurrent modality demands. We will explore visual and auditory attention using unimodal tasks based on the criteria of Posner et al (1982), and divided attention using novel dual modality methodology. Our method is similar to McCarthy et al, (2005) insofar as our approach is a departure from established tests of divided attention and reflects our interest in establishing whether central executive attentional deficits are revealed by a novel dual modality test. This test utilises simpler perceptual stimuli and restricts an over involvement of motor and associated cognitive processing demands on participants. Participants must divide their attention between a visual input and an

auditory input, which is combined into a choice response. Our general hypothesis is that MS participants will show an impairment in the central executive component of attentional control reflected by an experimental decrement compared to controls involving higher latency response times and increased error scores within the bimodal divided attention task.

The paradigms developed fit within the construct of working memory proposed by Baddeley, (1986) and are in line with his suggestions for investigating the central executive component of working memory (Baddeley et al, 1997). Further, Sarter & Turchi, (2002) describe divided attention as the ability to divide resources between multiple and competing perceptual tasks. The tests in this study are designed to isolate the attentional system using multiple and competing perceptual tasks. Across the tasks cognitive load does not vary, with the same number of stimuli delivered within each trial. Therefore, the paradigms ensure that various attentional characteristics are examined, while maintaining a parity of cognitive load and information processing between tasks.

Hypotheses

The specific hypotheses are:

1) MS participants will not differ from controls on modality specific single tests of attention.

2) MS participants will show poorer performance on bimodal divided attention tests, compared to controls.

Plan of Investigation

Participants:

The study will aim to recruit participants with multiple sclerosis and a non-clinical, age and education matched control group. The MS group will be in the early stages of the disease with mild impairment, as defined by their EDSS score (Kurtzke, 1983). Therefore, we are considering patients with a diagnosis of less than 5 years with an EDSS score of 3 or less (which reflects minimal motor disability). The EDSS is a 20-point rating scale, which is widely used in MS research samples, and rates the level of physical disability of a participant. The participants will be in the age range of 25-40 years, which is linked with the mean age of onset and early stages of the disease. Using a lower EDSS score and minimum time since diagnosis will enhance the clinical homogeneity of the clinical group and facilitate the research question of interest in investigating MS in the early stages. Other inclusion criteria will also specify that the MS group are of the same disease type (relapsing-remitting type) with a disease status in remission.

The participants will have no co-morbid neurological or psychiatric conditions, and no gross motor defects, or hearing or eyesight deficits. Visual acuity will be checked using the Cortical Vision Screening Test (CORVIST) (James, Plant, Warrington, 2001) and a colour vision test using Ishihara Colour Plates will be carried out. Brief neuropsychological assessment using the Wechsler Test of Adult Reading, and Addenbrooke's Cognitive Examination will be used with appropriate cut-off scores established, excluding participants with significant cognitive impairment.

In addition, the mood and anxiety of the participants will be assessed using the Depression Anxiety Stress Scales (DASS), (Lovibond and Lovibond, 1995).

Recruitment:

The MS group will be recruited from the clinic of the lead MS Consultant Neurologist at the department of Neurology, Southern General Hospital, Glasgow. Advice on participant selection has been given and access to MS participants will be gained once the neurologist has selected suitable participants from the case notes based on our inclusion criteria. The feasibility of recruiting the clinical numbers required has been discussed and agreed. In order to recruit the control group, an age matched friend or relative of each member of the clinical group will be invited to participate in the study. If this method fails to secure the required number of controls, then a recruitment advert will be placed locally within the Southern General Hospital, Glasgow. The study is aiming to recruit a total of 34 participants (17 patients and 17 controls).

Measures:

Experimental measures will be quantitative behavioural data including error and latency data. Specifically, reaction time data to presented stimuli and accuracy rates to choice tasks will be collected. In addition, measures of current cognitive status and participant mood will be assessed.

Design and Procedures:

We are employing a between subjects design, comparing MS patients and non-clinical controls across three paradigms. The procedure will involve modality specific cognitive tasks performed singularly and a bimodal attention task. It is envisaged that each participant will take approximately 1 hour to complete all aspects of the experiment and to minimise fatigue effects, experiments will be conducted in the morning. The project will be carried out at the one site, namely the Southern General Hospital and laboratory space within the Sackler Research Centre has been allocated for the study.

Three experiments will be delivered via a Windows PC using Superlab Pro (Version 2) experimental software. These paradigms have been designed to investigate a 'central executive's' divided attention ability by targeting visual and auditory perceptual streams.

Visual Sustained Attention Task:

Visual spatiotemporal cue coupling paradigm

This task invokes sustained attention to spatial and temporal cues. On each trial, the participant is instructed to focus on a central fixation point (a black cross) on a PC monitor. Visual stimulus pairs (coloured boxes) are presented in succession and can appear in four different equidistant locations on the monitor (roughly corresponding to the four corner areas). The task is to decide as quickly as possible whether the two stimuli are the same (50%) or different (50%) colour. The stimuli appear in the same location (valid spatial cue) 80% of the time, and in a different location (invalid spatial cue) 20% of the time. Similarly, stimuli will appear at a highly predictable intrastimulus temporal interval (500msec; valid temporal cue) 80% of the time, and an

unpredictable interval (100, 200, 300, 400 msecs; invalid temporal cue) 20% of the time. Alignment of valid cues is predicted to produce the best performance, measured by both response time and accuracy. Performance is predicted to decline when one cue is invalid, and decline more when both cues are invalid.

The experiment will have 2 blocks with 50 randomised trials per block. A button box will be used to collect participant responses, which will be key presses with the index finger of both hands. Experimental data will be stored anonymously for later combined analysis.

Auditory Sustained Attention Task

Auditory spatiotemporal cue coupling

This task is an auditory analogue to the visual task above. On each trial, two tones are presented by the PC, in succession through stereo headphones. The task is to decide whether the tones (created at 500 hertz, 800hertz, 1000 hertz, and 1500 hertz) are identical (50%) or not (50%). The tone stimuli are presented in the same ear (valid spatial cue) 80% of the time, and in different ears (invalid spatial cue) 20% of the time. Stimuli will be 150 msec long, separated by 500msec 80% of the time (valid temporal cue), and by a varying interval (100, 200, 300, 400 msec) 20% of the time (invalid temporal cue).

As before, performance, measured in response times and accuracy, is predicted to be a function of cue alignment. The experiment will have 2 blocks with 50 randomised

trials per block. A button box will be used to collect participant responses, which will be key presses with the index finger of both hands. Experimental data will be stored anonymously for later combined analysis.

Divided Attention Task

Visuo-auditory spatial matching task

This task will combine the elementary perceptual units used in the visual and auditory tasks to create a test of divided attention, a visuo-auditory, spatial matching task. Participants will be required to simultaneously attend to auditory and visual information and combine this to make an informed reaction time choice on spatial matching. On each trial, a visual stimulus (coloured box) and tone are presented in succession. The task is to decide whether the stimuli are presented in the same spatial location (50%) of the time or different (50%). For example, the same spatial location would be a tone being heard in the left ear and a coloured box appearing on the left side of the screen. The valid intra-stimulus temporal cue will be (500msecs) 80% of the time and the invalid temporal cues will be (100, 200, 300, 400 msecs) 20% of the time. The experiment will have 2 blocks with 50 randomised trials per block.

The sequence of presentation of stimuli will be tone-visual 50% and visual-tone 50%. A button box will be used to collect responses, which will be key presses with the index finger of both hands. Experimental data will be stored anonymously for later combined analysis.

Settings and Equipment:

The setting will be a laboratory room within the Sacker Research Centre at the Southern General Hospital, Glasgow, that is free from outside distraction. Equipment will include paper and pencil tests (WTAR, CORVIST, Addenbrooke's Cognitive Examination, and DASS), use of a Windows PC, button box, monitor, stereo headphones, and Superlab Pro (Version 2) experimental software. Also, Ishihara Colour Plates will be used.

Power Calculation:

A recent study examining modality specific aspects of sustained and divided attention in MS recruited 30 MS participants and 30 neurologically intact healthy controls (McCarthy et al, 2005) and found a statistically significant difference between the MS group and control group. The effect size calculated from their reaction time data on the bimodal divided attention task was 1.18, with power calculated as 0.998. It is reasonable to assume that the present study will have a similar effect size with a significance level of alpha = 0.05. The sample sizes required are 17 participants from the MS group and 6 participants for the present study to have a power of 0.9. The present study will recruit an equal number from each group and recruit a minimum of 17 participants from the MS and control group, giving a total of 34 participants.

Data Analysis:

Descriptive and inferential statistics will be employed to explore response time and response accuracy scores. Summary data including means and standard deviations will be tabulated and described for the participants' reaction times and accuracy rates

across all three tasks. Further, Analysis of Variance (ANOVAs) will be calculated with group and tasks being the main factors. Performance between groups will be investigated for all three tasks and performance between tasks within groups will be investigated. Post-hoc analysis will be used to investigate where potential differences lie.

Practical Applications

Results will add to the existing body of literature in this field and hopefully provide useful information for understanding the cognitive attentional profile in early multiple sclerosis. Also, the paradigms designed here may prove useful for researching aspects of attention in a neurological population and their validity and reliability as tools for investigating attention will be explored. Further, results may have practical implications for patients and may have the potential to inform some aspects of clinical practice. For example, if MS patients have difficulty with attending to more than one thing at a time, there are obvious implications for the practice of delivering complex information and daily living advice to patients within the clinic. A compromised attentional system may contribute to impaired memory and the ability to acquire and retrieve complex information. Therefore, investigations such as this one could inform future practice guidelines. Further, studies (Ling, 2002; Schultheis et al, 2001) have suggested that cognitive dysfunction in MS may contribute to a decrease in driving ability and higher rates of vehicle crashes. The present study may further elucidate where difficulties in attending to competing stimuli occur.

Timescale

The project is aiming to work comfortably within the parameters of the published MRP guidelines and deadlines. It is envisaged that demo versions of the experimental paradigms will be programmed by April 2006 and full working versions of the paradigms by June 2006. Submission to the ethics committee will be done by May 2006. It is expected that recruitment packages will be sent to potential participants in July 2006 with experimental running commencing in September 2006 and be completed by February 2007. Following this, data analysis will be executed with a first draft of the project expected for April 2007.

Ethical Approval

This will be required and submission will be made to the local ethics committee before any potential participants are approached. No obvious ethical issues have been identified at this stage.

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Chapter 4: Major Research Project

Visual, auditory, and divided attention ability in early stage relapsing remitting multiple sclerosis. An investigation using novel dual modality paradigms.

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(See Appendix 3.6 for contributor's notes)

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Abstract

The cognitive impairment profile in multiple sclerosis has been well documented, however less is known about the nature of cognitive changes in early stage relapsing remitting multiple sclerosis. The ability to sustain and divide attention is a complex and demanding cognitive process utilizing dedicated cortical areas involving reciprocal short and long distance intact connections. Such processes are vulnerable to disruption following axonal changes such as those in multiple sclerosis. Using novel computer based paradigms, 17 relapsing remitting multiple sclerosis patients and 17 healthy controls, participated in unimodal and bimodal visual and auditory attention paradigms. Contrary to our hypotheses, the multiple sclerosis group were not impaired relative to controls across all variables. Both groups displayed an expected performance decrement during bimodal divided attention tasks but only in relation to the auditory task. These results indicate that cognitive processes, as assessed by this task, remain intact in the very early stages of relapsing remitting multiple sclerosis. This suggests that detectable cognitive impairment, especially the attentional network, is the result of protracted and sustained damage to multiple subcortical white matter tracts, which are not evident in the disease pathology at this early stage of diagnosis.

Introduction

Multiple sclerosis (MS) is a neurodegenerative inflammatory demyelinating condition of the central nervous system with a variable clinical course involving several disease subtypes. Multiple sclerosis means 'many scars' and disease progression follows four main subtypes, however the most common subtype is relapsing-remitting multiple sclerosis, characterised by acute attacks of neurological dysfunction, followed by partial or complete recovery (SNAP, 2000). In addition, prevalence rates are calculated at 144 cases per 100,000 of the population in the West of Scotland. The pathology and ensuing disability is linked with the process of axonal demyelination, remyelination, and axonal and synaptic degeneration (Orhun et al., 2005). The accumulating lesion profile in the brain is diffuse, affecting central nervous functioning, motor systems, and multiple brain regions. The clinical manifestation of the disease varies considerably between sufferers and is related to lesion site, lesion load, and subsequent effects on function.

In addition to the physical problems experienced, cognitive impairment in MS is well documented and estimates of cognitive deterioration in patients range from 45 – 65%, (Rao, 1995). The nature and course of MS is heterogeneous and recognized cognitive deficits involve a range of domains including memory, attention, and speed of information processing (Zakzanis, 2000). Lezak, (2005) reports common circumscribed deficits in the cognitive domains of attention, memory, and executive function in relapsing-remitting patients. Spilich, Mubrin, and Janculjak (2002) state that changes in cognitive processes may appear long before the physical

manifestations of MS, suggesting that identifying patients earlier could be based on cognitive changes. However, there are difficulties in identifying unique cognitive markers for any neurological condition, especially in the early stages due to overlap in presentation.

Even though the cognitive profile in MS is often heterogeneous, a consistent deficit found in multiple sclerosis are problems with attention and the ability to attend to more than one thing at the same time which is known as divided attention (Bobholz & Rao, 2003). In addition, an intact attentional system is vital for the efficient processing of other various cognitive systems, for example memory encoding. There is some suggestion that deficits in higher cognitive operations are actually secondary to primary attentional problems in MS. However the extant MS literature examining attentional dysfunction leaves unanswered questions as to the extent and nature of deficits (McCarthy et al., 2005).

When considering the concept of attention there are various theoretical cognitive models of attention and one of the most influential and frequently referenced theories is Baddeley's, (1986) working memory model. He proposed a structural model involving multiple interactive components including a central executive controller that regulates and distributes the limited available attentional resources that a system possesses, and visuospatial and phonological slave systems (Baddeley, 2003). The slave systems are responsible for storage of modality specific inputs and one of the principle roles of a central executive system would be to efficiently allocate and

manage attentional resources when two or more tasks are being executed simultaneously or when attention is divided between the visual and auditory slave systems (Baddeley, 1996).

Dual tasking or divided attention paradigms have been used extensively to study this fundamental property of an executive control system in various patient populations (Baddeley et al., 1997). Dual tasking designs involve performing two different tasks on their own and then concurrently, and comparing performance levels on one or more of the tasks. For example, established formats involve participants performing a verbal digit span task with a visual tracking task. In clinical populations, a dual task performance decrement is frequently observed and reported in the context of damage to an executive coordinator responsible for dividing and allocating attention; for example in Alzheimer's disease (Logie et al., 2004).

Further, Baddeley, Bucks, and Wilcock, (2001) found that Alzheimer's disease patients have a specific difficulty with dual task performance, even when controlling for the general overall cognitive demand, suggesting that available attentional resources is not the problem, but how they are allocated is. Also, in a frontal lobe lesion patient group Baddeley et al., (1997) found that patients with dysexecutive syndrome showed impaired capacity for dual tasking.

In multiple sclerosis, evidence indicates that the multifocal lesion profile may affect brain areas which form the working memory substrate, leading to working memory impairment in the early stages of the disease (Pelosi et al., 1997) and thus difficulties with focusing and dividing attention during task.

D'Esposito et al., (1996) investigated central executive functioning using dual tasking methodology comparing an MS group with a control group. In their study, the dual tasking paradigm involved performing a primary task concurrently with one of three secondary tasks. The primary task involved a line orientation judgement with the concurrent secondary tasks being finger tapping, alphabet recitation, and humming a melody. Results showed that the MS group performed less well during the more demanding dual task conditions (humming a melody and alphabet recitation) than the control group. The authors concluded that the dual task decrement found in the MS group, reflected an impaired central executive of working memory resulting in difficulty allocating sufficient attentional resources to support concurrent task execution. Certainly under such dual task conditions there is a higher cognitive load and recruitment of more specialist cognitive systems such as memory, visuospatial ability, and even musical performance. However, conclusions that it is attention that is breaking down has to be questioned as the task decrement could be explained by a breakdown in any one of the cognitive processes involved and not just attention. The fundamental properties of the central executive are attentional modification to task presence. Isolation of this fundamental should be aimed for when examining divided attention. Baddeley et al., (1997) states that paradigms exploring the central executive's coordination properties should involve simultaneous operation of the phonological loop and visuospatial sketchpad. This doesn't equate to tasks such as

those used by De'Esposito et al., (1996) that recruit higher cognitive functions of language, memory, and musical ability, and fail to isolate the basic properties of the working memory model.

Paul et al., (1998) investigated several aspects of automatic and controlled attentional processing in MS using tests of focused and divided attention. They used the Posner spatial attention task (Posner, Cohen, & Rafal, 1982), which involves visual stimuli presented with valid and invalid spatial cues, as a test of automatic processing and found that the MS group performed as well as the control group. The Paced Auditory Serial Addition Task (PASAT) was used as a test of divided attention in this study and the MS group performed significantly worse than the controls. Whether the PASAT is truly a test of divided attention is worthy of thought as the nature of that task involves sustained attention over time with higher cognitive functions of calculation recruited. Often, the PASAT is used as an index of information processing speed and clearly, there is a large working memory involvement, but it is questionable whether this test fulfils the criteria that Baddeley, (1997) suggests for divided attention methodology.

Recently, McCarthy et al., (2005) considered the profile of attentional dysfunction in MS using divided and sustained attention methodology across unimodal and bimodal visual and auditory trials. The authors developed two new measures of sustained and divided attention as part of their study and recognised that their approach to investigating divided attention was in contrast with conventional dual tasking methodologies where primary task decrement is measured during concurrent

secondary task execution. In the divided attention task, targets were digits that were consecutive pairs either ascending or descending with a temporal delay between digit presentations in a trial. Participants were required to divide their attention between retention of the first digit and presentation of the next digit. Thirty MS participants were compared with 30 controls across all six conditions (sustained vs divided task and auditory, visual, bimodal presentations). The results suggested that the MS group performed slower and less accurately than controls on both sustained and divided measures of attention. Of note, the MS group were disproportionately slower on the bimodal trials of the divided attention task, relative to unimodal trials. The authors concluded that their results were not related to motor slowing or information processing speed deficits, but linked with the task demands and the modality targeted. When the MS group were performing the divided attention task in visuo-auditory bimodal trials, their performance suffered most and this could be explained within Baddeley's, (2003) theoretical framework with a deficient central executive component, impaired in allocating attentional resources efficiently between visual and auditory modalities.

The aim of this present study was to further understand the nature of cognitive impairment in multiple sclerosis, and in particular to investigate the attentional system in the early stages of the relapsing remitting disease type. Specifically, we were interested in the ability to divide attention during concurrent modality demands. We explored visual and auditory attention using unimodal tasks based on the criteria of Posner et al., (1982), and divided attention using novel dual modality methodology. The method is similar to McCarthy et al., (2005) insofar as the approach was an attempt to depart from established tests of divided attention and reflects our aim of

establishing whether central executive attentional deficits are revealed by a novel dual modality test. This test utilised simpler perceptual stimuli and restricts an over involvement of motor and associated cognitive processing demands on participants. Participants had to divide their attention between a visual input and an auditory input, which was combined into a choice response. Our general hypothesis was that MS participants would show an impairment in the central executive component of attentional control reflected by an experimental decrement compared to controls involving higher latency response times and increased error scores within the bimodal divided attention task.

The paradigms developed fit within the construct of working memory proposed by Baddeley, (1986) and are in line with his suggestions for investigating the central executive component of working memory (Baddeley et al., 1997). Further, Sarter & Turchi, (2002) describe divided attention as the ability to divide resources between multiple and competing perceptual tasks. The tests in this study were designed to isolate the attentional system using multiple and competing perceptual tasks. Across the tasks cognitive load did not vary, with the same number of stimuli delivered within each trial. Therefore, the paradigms ensured that various attentional characteristics were examined, while maintaining a parity of cognitive load and information processing between tasks.

Methods

Participants:

Seventeen patients (5 males) diagnosed with relapsing remitting multiple sclerosis were recruited from a clinic-based sample of the West of Scotland Multiple Sclerosis Service. Seventeen (5 males) age and education matched healthy controls were recruited from the local area and using spouses and friends of the clinical sample. All patients had an expanded disability status score (EDSS) of less than 3 which reflects a minimal level of motor disability and sensory and physical disturbance (Kurtzke, 1983). The patients were in the early stages of the disease and all had a diagnosis of relapsing remitting multiple sclerosis of less than 3 years at the time of the study. There were no psychiatric or neurological comorbidities within the group and only patients without optic neuritis or hearing impairments were included. All had normal or corrected to normal vision and were in remission at the time of study. Although no formal record of individual pharmacotherapy use was detailed, some of the patient sample were on disease modifying treatment at the time of the study. No payment, apart from minor traveling expenses, was offered to the participants. Ethical approval was obtained from the Local Research and Ethics Department and informed consent was given by each participant. Characteristics of the sample are given in (Table 1).

The sample size was decided on from a recent study examining modality specific aspects of sustained and divided attention in MS where the authors recruited 30 MS participants and 30 neurologically intact healthy controls (McCarthy et al, 2005). They found a statistically significant difference between the MS group and control group. The effect size calculated from their reaction time data on the bimodal divided

atention task was 1.18, with power calculated as 0.998. It is reasonable to assume that the present study will have a similar effect size with a significance level of alpha =0.05. The sample sizes required are 17 participants from the MS group and 6 control participants for the present study to have a power of 0.9.

Table 1: Sample Characteristics

	Sample	Age	Education (Years)	Diagnosis duration
Controls	17	30.9 (5.5) Range = 22 - 40	Mean = 13.8	Not applicable
Patients	17	32.06 (5.6) Range = 22 - 40	Mean = 12.47	14.7 (13.5) months Range = 2 - 36

Neuropsychological Measures:

All participants completed a neuropsychological screening battery to assess any gross deficits. Visual acuity was checked using the Snellen Chart, Visual Object and Space Battery, and a colour vision test using Ishihara Colour Plates. None of the participants had any hearing problems. Premorbid intellectual functioning was assessed using the Wechsler Test of Adult Reading. The Addenbrooke's Cognitive Examination was used as a multi domain cognitive screen and the mood and anxiety of the participants was assessed using the Depression Anxiety Stress Scales (DASS) and scores compared to established norms (Lovibond and Lovibond, 1995). Summary scores are given in (Table 2).

Table 2: Summary neuropsychological results

	Snellen results	Ishihara Colour Vision	Predicted full scale IQ	ACE Screen	VOSP	DASS
Controls	Snellen visual acuity of 6/6 or better	100% sample passed	109.7 (5.3) Range = 110 - 119	96.1 (2.4) Range = 91 - 100	All subtests passed	Non-significant
Patients	Snellen visual acuity of 6/6 or better	100% sample passed	107.7 (4.4) Range = 98 - 114	95.1 (3.1) Range = 89 - 100	All subtests passed	Non-significant

Experimental Measures and Design:

The experiments were delivered via a Windows PC using Superlab Pro (Version 2) experimental software. Reaction time data and error rates were calculated for each participant across three different paradigms consisting of 100 experimental trials in each paradigm. A between subjects design was used to compare performance of both groups across tasks: repeated measures (2 x 3) analysis of variance. The tasks consisted of a visual task, an auditory task, and a combination of both. In the visual condition, on each trial the participant was instructed to focus on a central fixation point (a black cross) on a PC monitor. Visual stimulus pairs (coloured boxes) were presented in succession and could appear in four different equidistant locations on the monitor (roughly corresponding to the four corner areas). The task was to decide as quickly as possible whether the two stimuli were the same (50%) or different (50%) colour. Intrastimulus temporal rates and spatial locations were varied to ensure focused attention and minimise automatic responding. All stimuli had a maximum screen duration of 150msecs which prevents ocular saccades. The auditory condition was analogous to the visual condition in design with two tones presented on each trial requiring a pitch similarity decision.

Divided Attention Task

Visuo-auditory spatial matching task

This task combined the elementary perceptual units used in the visual and auditory tasks to create a novel test of divided attention, a visuo-auditory, spatial matching task. Participants simultaneously attended to auditory and visual information and combined this to make an informed reaction time choice on spatial matching. On each trial, a visual stimulus (coloured box) and tone was presented in succession. The task was to decide whether the stimuli were presented in the same spatial location (50%) of the time or different (50%). For example, the same spatial location would be a tone being heard in the left ear and a coloured box appearing on the left side of the screen. The sequence of presentation of stimuli was tone-visual 50% and visual-tone 50%. Intrastimulus temporal rates were varied on 20% of the trials to allow analysis of a subset of invalid trials.

Procedure

All participants were assessed at the University of Glasgow Sackler Institute, Southern General Hospital, Glasgow in a sound proof sleep laboratory which was climate controlled. Ambient lighting was minimal allowing maximum awareness of monitor emission. The author (SM) administered all the vision and neuropsychological tests before giving standard instructions on the three computer based paradigms. These paradigms were delivered by a Toshiba Satellite Pro computer running SuperLab experimental software which had been programmed to produce the experimental paradigms. For the auditory and divided attention tasks, participants wore a Hitachi stereo headphone set.

Participants sat approximately two feet from the monitor and instructions appeared on screen before each experiment commenced. This was followed by 10 practice trials and then each participant was given the opportunity to ask any further questions before beginning the experimental trials. The participants were left in the room on their own while the experimental trials were running to ensure maximum concentration. The experimenter viewed the participants via a remote video camera during the experiment and all participants were made aware of this. At the end of each paradigm the software automatically stopped, the participant raised their hand, and the experimenter returned to the laboratory and started the next experimental trial group. This ensured a standardized procedure for each participant.

Results

There was no difference between groups in terms of age ($t = -0.58$; $p = 0.563$) or years of education ($t = 0.46$; $p = 0.482$). Comparison of premorbid intellectual level using WTAR predicted full scale IQ showed no differences between groups ($t = 1.162$; $p = 0.254$). All participants passed the Snellen visual acuity test, Ishihara colour vision test, and the subtests of the visual object space perception battery. No participant had clinically significant levels of depression, anxiety or stress as defined by the (DASS). There was no difference between groups on the Addenbrooke's Cognitive Examination screening score ($t = 1.04$; $p = 0.306$).

Reaction time data:

The mean reaction times for both groups across all three paradigms were calculated. Table 3 details the summary descriptives with (Figure 1) offering a visual display of mean reaction times for both groups.

Figure 1: Graph of control and patient reaction times across all three attention paradigms

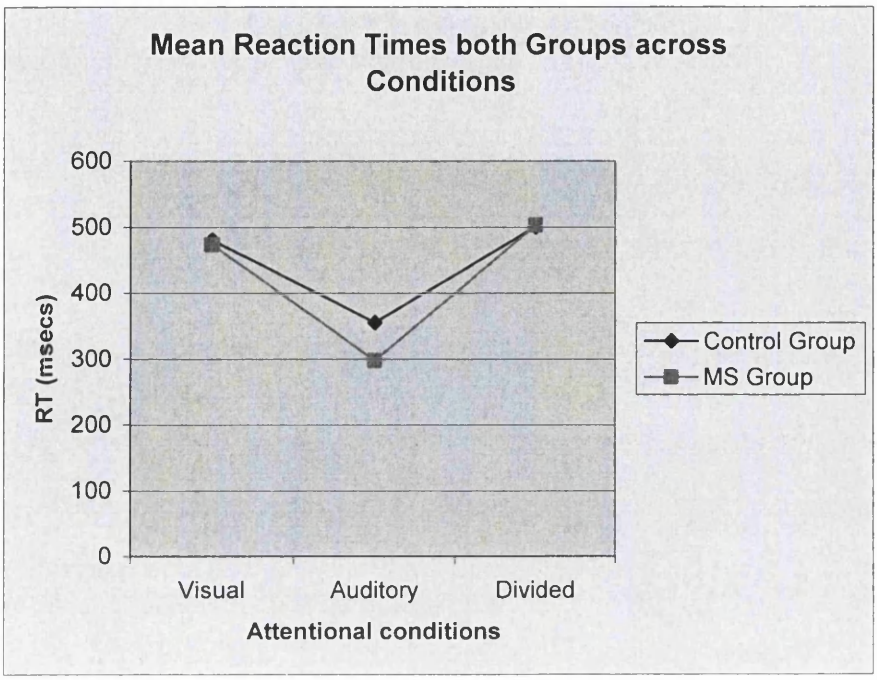


Table 3: Summary reaction time statistics for patient and controls across all three tasks

Participant	Paradigm	Mean (msecs)	Standard Deviation
Control	*Visual*	480.3	140.5
	Auditory	355.2	153
	Divided	500.9	155.2
MS Group	*Visual*	473.3	96.8
	Auditory	297.9	125.5
	Divided	503	107.6

The distribution of the reaction time data was analysed for the assumption of Normality using the Shapiro-Wilk statistic. The MS group reaction time data for the visual and auditory paradigms was Normally distributed but not for the divided attention task. The control reaction time data was Normally distributed for all three paradigms. Due to there being equal sample sizes in each group and a homogeneity of variance the ANOVA was selected for inferential analysis.

A repeated measures ANOVA (2 x 3) was used to analyse the data. There was no statistically significant difference between controls and patients across tasks for reaction times ($F = 1.154$; $p = 0.328$) with an effect size (partial Eta squared = 0.069). Therefore there was no significant interaction. There was a statistically significant main effect of paradigm ($F = 40.669$; $p < 0.0001$). Multiple comparisons using the Bonferroni method with statistical significance at ($p = 0.05$) revealed statistically significant differences in the control group between the visual task and the auditory task ($p = 0.03$) and the auditory task and the bimodal task ($p = 0.001$). In the patient group multiple comparisons using the Bonferroni method with statistical significance at ($p = 0.05$) revealed statistically significant differences between the visual and auditory tasks ($p < 0.0001$) and auditory and bimodal task ($p < 0.0001$).

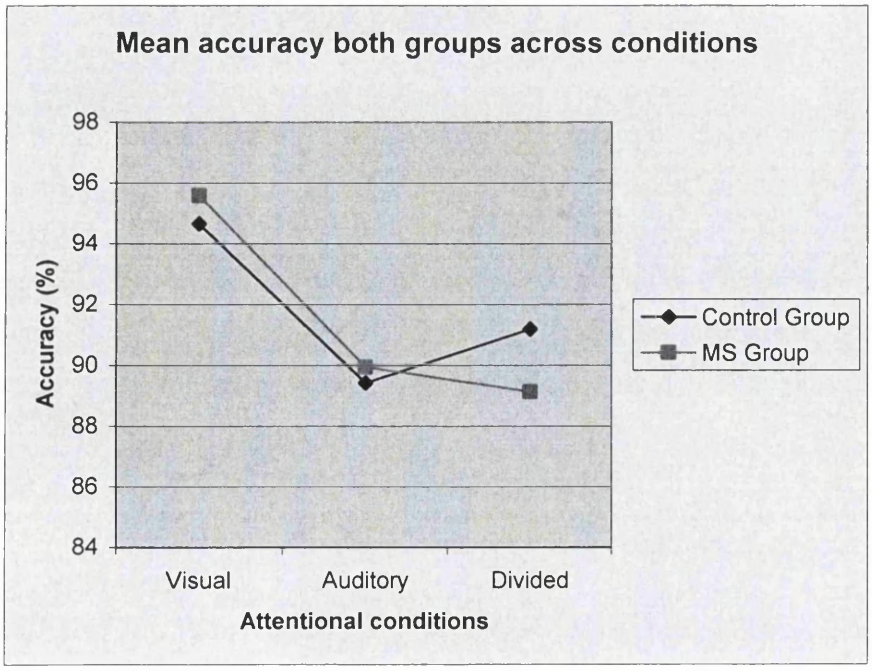
Error Data:

The mean error rates for both groups across all three paradigms were calculated. Table 4 details the summary descriptives with (Figure 2) offering a visual display of mean error rates for both groups.

Table 4: Summary error statistics for patient and controls across all three tasks

Participant	Paradigm	Mean Accuracy (%)	Standard Deviation
Control	*Visual*	94.6	3.1
	Auditory	89.4	7.5
	Divided	91.2	6.9
MS Group	*Visual*	95.6	2.7
	Auditory	89.9	13.1
	Divided	89.1	10.1

Figure 2: Graph of control and patient reaction times across all three attention paradigms



The distribution of the error data was analysed for the assumption of Normality using the Shapiro-Wilk statistic. The MS group error data for the visual paradigm was Normally distributed but not for the auditory or divided attention data. The control error data was Normally distributed for all three paradigms. Due to there being equal sample sizes in each group and a homogeneity of variance the ANOVA was selected for inferential analysis. In the control group there was a statistically significant main effect of paradigm ($F = 3.852$; $p = 0.045$). Multiple comparisons using the Bonferroni method with statistical significance at ($p = 0.05$) revealed statistically significant differences between the visual task and the auditory task ($p = 0.037$) but not the auditory task and the bimodal task ($p = 0.983$). In the patient group there was a statistically significant main effect of paradigm ($F = 4.881$; $p < 0.023$). Multiple comparisons using the Bonferroni method with statistical significance at ($p = 0.05$) revealed no statistically significant differences between the visual and auditory tasks ($p = 0.213$), visual and bimodal task ($p = 0.058$), or auditory and bimodal task. This was due to the alpha level correction inherent in the Bonferroni calculation. There was no statistically significant difference between controls and patients across tasks for errors ($F = 0.469$; $p = 0.63$) with an effect size (partial Eta squared = 0.029), therefore there was no significant interaction.

Divided Attention Paradigm: Invalid Trials:

The mean reaction times and error levels for the divided attention paradigm invalid trials for both groups are given in table 5.

Table 5: Summary error statistics for patient and controls for divided attention paradigm invalid trials

Participant	Mean reaction time (msecs)	Mean accuracy (%)
Control	512.72 (164.53)	92.0 (6.4)
MS Group	536.83 (129.1)	89.2 (12.4)

The mean reaction time for the control group was faster and they made fewer errors than the MS group, however there was no significant difference found between groups for reaction time ($t = -0.475$; $p = 0.638$) or errors ($t = 0.831$; $p = 0.412$).

Discussion

The purpose of this study was to investigate cognitive changes in early stage relapsing remitting multiple sclerosis. In particular, ability to divide attention between multiple perceptual streams was explored. The specific hypotheses were that the MS group would attain a similar level of performance as the control group during unimodal visual and auditory tasks and show a disproportionate decrement in performance compared to controls on the test of divided attention involving bimodal attention. This performance decrement would be recorded as an increase in error rates and increased response latency. The attentional tasks used were in-house designed measures of visual attention, auditory attention, and visuo-auditory attention. These tasks were designed to minimize excessive motor demands that could confound reaction time data and focus as much as possible in isolating pure attention avoiding other cognitive processes. The target of interest was the central executive component of Baddeley's (1986) working memory model that is thought to be responsible for allocating and monitoring attentional resources.

Our first hypothesis that there would be no significant difference between patients and controls on unimodal attentional measures was supported with both reaction times and error rates. There was no statistically significant difference found. During divided attention conditions using the bimodal spatial matching task, there was no statistically significant difference between the patient group and controls.

The effectiveness of the designed paradigms was demonstrated within both the controls and the MS group with both groups benefiting significantly when auditory stimuli were presented in isolation. This led to facilitation in response latency with both groups on average producing their fastest performance in task decision. When visual information was added to the auditory component to create the bimodal divided attention task, both groups were significantly slower in responding to stimuli compared to the auditory task but not the visual task. Interestingly, the opposite was found in the error data with unimodal auditory conditions producing the least accurate performance and unimodal visual conditions producing the most accurate response. Therefore, under visual conditions, both groups were slower but more accurate, and under auditory conditions, both groups were faster but less accurate. In the patient group there was a trend to be slowest and least accurate in the divided attention paradigm.

The question of why no statistically significant difference between groups was found has to be addressed and there are several possible explanations that may explain this lack of difference. Firstly the multiple sclerosis group studied here are unquestionably within the very mild spectrum of the disease. All patients were in the early stages of relapsing remitting disease and outwith relapse at time of study. Their cognitive functioning was intact and some were on disease modifying therapy, which has a protective function with regards disease process including cognitive functioning (Fischer et al., 2000).

MS is characterized by lesions within the cerebral hemispheres with a predilection for periventricular locations (Rovaris, Comi, & Filippi, 2006). However the lesion profile is not predictable and there is great variability between patients as to the location and number of lesions within the brain. In the early stages of MS it is likely that there will be fewer lesions within the brain and therefore the chances of a cognitive system being damaged is lower. Also, in some patients with a longer duration of illness, cognitive impairment has been found to be absent, again highlighting the variability within this complex disorder. It is likely that the patient group studied here had a minimal lesion load. Further, cognitive impairment in MS has been associated with cerebral atrophy and studies have found links between cognitive performance and neural volume decrease of the MS brain using the brain parenchymal fraction. Again, this type of atrophy is unlikely to be present in this patient group with such a short length of diagnosis as atrophy of neural structure takes time to occur.

Further, recent fMRI evidence during working memory tasks in MS suggests that there is compensatory recruitment of additional brain areas early on in the disease process and it is possible that this retaliative neural recruitment supports delay in cognitive demise (Au Duong et al., 2005). Therefore, any cognitive changes that are present within this group may be so mild that statistical significance cannot be found but trends in the data can; which is what we found in the divided attention latency and error data results. The majority of the MS group had been through higher education and attained degrees and some research (Pinn, 2001) suggests that higher levels of education act as a "buffer" effect in relapsing remitting MS particularly buffering against loss of executive functioning.

Previous research that has found divided attention deficits in MS and other neurological or dementing disorders has usually used dual tasking methodology, which involves tasks of greater complexity than those used in this study. More often, dual tasking methodology has a more significant motor component involved in the tasks and it may be this process that is largely responsible for the decrement in performance found in these studies. In line with this observation it is likely that the paradigms designed here were not sufficient in terms of the cognitive load they exerted on the patients and therefore did not reveal cognitive changes that were present. While neither group hit a 'ceiling effect' in terms of accuracy performance, both groups did perform at a consistently high level of accuracy, which may reveal task simplicity.

The unimodal and divided attention tasks devised for this study were built with three integral points central: minimal motor demands across tasks, parity of cognitive load across tasks, and isolation of pure attention with minimal involvement of higher cognitive processes. Using tasks with a minimal motor component reduces the confounding variable of peripheral muscular slowness, which can by proxy affect cognitive measures giving an artificial assessment of cognitive functioning. A homogeneity of cognitive load was essential to ensure that, during the divided attention task, any decrement in performance was not just the result of increased task difficulty when doing two things at the same time, but a genuine breakdown when attention is split between bimodal perceptual streams. Therefore performance decrement could be attributed to a faulty attentional controller.

This is a common complaint of existing dual tasking methodology, which purports to measure divided attention.

This methodology usually involves combining tasks with a motor component, for example walking, with a cognitive task like digit span or PASAT. These cognitive tasks arguably involve more cognitive processes than just attention. Perhaps in trying to focus on the attention system as purely as possible, the paradigms within this study may have tapped into perceptual processes much earlier in the stimulus to brain pathway and did not adequately tax the attention system itself. Potentially, a divided attention deficit in early stage relapsing remitting MS may be present.

The tasks used were built on basic perceptual units: coloured shapes, and simple tones. It may be that such stimuli can be recognized and computed at a purely perceptual level within the ventral and dorsal stream visual pathways and requires little if any involvement of a central executive attentional controller which is assumed to be subserved by neural substrate within the frontal cortices. Further, the divided attention part of this experiment involved the auditory and visual stimuli being presented serially, albeit with a very short (<500msecs) intrastimulus interval. This delay may have been long enough for the cognitive system to process the first stimulus before the other arrives and this would then negate the purpose of involving a divided attention system, regardless of whether the stimuli being registered comes from two different sensory modalities.

Despite the heterogeneity of MS a consistent finding within the literature is that 40-65% of patients will develop attentional problems of some kind. However what is less clear is the extent of the causal variables that contribute to this impairment. For example, it is accepted that white matter lesions can reduce speed of processing in the MS brain. These lesions damage the myelin sheathes leaving denuded axons that cannot efficiently execute saltatory conduction meaning neuronal signals have a decreased velocity and increased signal transit time. If the brain processes involved in cognition are assumed to operate within synchronous firing patterns whose orchestration and timely arrival are the bedrock of efficient performance, then it is not surprising that this then has a secondary effect on attentional systems. These systems are assumed to be subserved by a complex network of distant brain regions traveling between frontal, subcortical, and parietal cortices. Further, lesions in the cognitive-motor pathways can affect speed and automaticity of simple and complex movements, which are involved in many cognitive tasks. Also, the powerful effects of fatigue on cognition cannot be discounted and many patients testify to experiencing cognitive decline during times of fatigue.

Perhaps then the attentional problem found in MS is actually multifactorial with different causal variables with different weightings depending on context rather than simply isolated damage to an attentional controller. It may be then that under experimental conditions, deficits in attention will only be highlighted when cognitive tasks involve a motor component, having to work at speed, or most likely a combination of both. If disconnection or slowing of connections between distant brain areas is the fundamental problem in the MS brain then simple tasks such as those used in this study will be less likely to create a 'bottleneck' in processing

information. The results found in this study will add to the existing body of literature in this field and hopefully provide useful information for understanding the cognitive attentional profile in early relapsing remitting multiple sclerosis and give pointers for future research.

The tasks devised for this study are not without merit and future studies are required to evaluate the paradigms. Studies could employ the divided attention paradigm to examine whether it is sensitive in detecting any differences in divided attention between different MS subtypes, as it is widely recognized that patients with the secondary progressive type of MS experience the greatest cognitive sequalae of the disease. For example, performance between relapsing remitting, secondary progressive, and primary progressive subtypes could be compared. Also, the performance of MS patients with and without cognitive impairment could be compared to evaluate whether the divided attention paradigm can discriminate between the cognitively impaired and cognitively intact patients. Perhaps the tests used here may be sensitive in detecting this cognitive impairment in the early stages and may be useful in tracking progression of the cognitive impairment over time.

In conclusion, there are no definitive methods of isolating and testing divided attention processes in multiple sclerosis and consensus on optimal procedures is required for future research of divided attention.

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Chapter 5: Single Case Research Proposal

Rehabilitation of impairment of facial expression perception in prosopagnosia

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Abstract

Prosopagnosia is an inability to recognise familiar faces and is the result of damage to brain pathways involved in complex visual processing. Attempts to rehabilitate identity recognition have proved inconclusive. Evidence suggests that facial identity recognition and recognition of facial expression are mediated by separate brain regions with the latter linked to featural processing rather than facial configuration processing. A prosopagnosic patient, X, was administered a comprehensive neuropsychological battery including a detailed investigation of his face perception abilities. X was severely impaired on all tests of facial identity recognition and impaired on emotional expression recognition. This study aims to rehabilitate the emotional expression recognition impairment using a face feature processing strategy. X will be trained to analyse face features and use these to identify facial expression. A multiple baseline design will be employed to systematically analyse the efficacy of the intervention.

Full chapter bound in Volume 2 of thesis

Appendices

Appendix 1.1 Guidelines for submission to Clinical Psychology

Notes to Contributors

- Articles of 1000-2000 words (including references) are welcomed. Send two hard copies of your contribution and also your e-mail address in case the editors need to contact you. Please do not send a disk or electronic copy until asked.
- When sending copy, make sure it is double spaced, in a reasonably sized font and that all pages are numbered.
- Give a 40-word summary (maximum) at the beginning of the paper.
- Contributors are asked to use language which is psychologically descriptive rather than medical and to avoid using devaluing terminology; i.e. avoid clustering terminology like 'the elderly' or medical jargon like 'person with schizophrenia'. If you find yourself using quotation marks around words of dubious meaning, please use a different word. If you do not wish to follow this guideline, please include a note explaining your particular use of language.
- We reserve the right to shorten, amend and hold back copy if needed.
- Articles submitted to *Clinical Psychology Forum* will be sent to members of the editorial collective for refereeing. We shall then communicate directly with authors.
- Include a word count at the end (including references).
- Spell out all acronyms the first time they appear.
  Include the first names of all authors and give their affiliations, and remember to give a full postal address for correspondence.
- Give references in the Society's style, and if a reference is cited in the text make sure it is in the list at the end.
- Don't include tables and figures unless they save space or add to the article.
- Ask readers to request a copy of your questionnaire from you rather than include the whole of it in the article.

Appendix 2.1 Guidelines for submission to Journal of the International Neuropsychological Society

JOURNAL OF THE INTERNATIONAL NEUROPSYCHOLOGICAL SOCIETY

Instructions for Contributors

Aims and Scope:

The *Journal of the International Neuropsychological Society* welcomes original, creative, high quality research papers covering all areas of neuropsychology. The focus of articles may be primarily experimental, more applied or clinical. Contributions will broadly reflect the interest of all areas of neuropsychology, including but not limited to: development of cognitive processes, brain-behavior relationships, adult and pediatric neuropsychology, neurobehavioral syndromes, such as aphasia or apraxia, and the interfaces of neuropsychology with related areas such as behavioral neurology, neuropsychiatry, and cognitive neuroscience. Papers that utilize behavioral, neuroimaging, and electrophysiological measures are appropriate. Book reviews will also be published.

To assure maximum flexibility and to promote diverse mechanisms of scholarly communication, the following formats are available in addition to *Regular Research Articles: Brief Communications* are shorter research articles; *Rapid Communications* are intended for "fast breaking" new work, that does not yet justify a full length article, and which are put on a fast review track; *Neurobehavioral Grand Rounds* are unique case studies, which are published in tandem with an introduction by an expert in the field to put the case into a more global perspective; *Critical Reviews* are thoughtful considerations of topics of importance to neuropsychology, including associated areas, such as functional brain imaging, neuroepidemiology, and ethical issues; *Dialogues* provide a forum for publishing two distinct positions on controversial issues in a point-counterpoint form; *Symposia* consist of several research articles that are thematically linked; *Letters to the Editor* respond to recent articles in the *Journal of the International Neuropsychological Society;* and *Book Reviews*.

Critical Reviews, *Dialogues*, and *Symposia* may be invited by the appropriate Department Editor or proposed by individual authors. Such proposals should be discussed with the Editor-in-Chief or the Department Editor before submission. *Book Reviews* are invited by the Book Review Editor.

Originality and Copyright

To be considered for publication in the *Journal of the International Neuropsychological Society*, a manuscript cannot have been published previously, nor can it be under review for publication elsewhere. Papers with multiple authors are reviewed with the assumption that all authors have approved the submitted manuscript and concur with its submission to the *Journal of the International Neuropsychological Society*. **A Copyright Transfer Agreement**, with certain specified rights reserved by the author, must be signed and returned to the Editor by the corresponding author of accepted manuscripts, prior to publication. This is necessary for the wide distribution of research findings, and the protection of both author and the society under copyright law.

Disclosure Form

An Author Disclosure Form must be signed by the corresponding author at the time the manuscript is submitted. This form includes an attestation that the manuscript is original and not under review in another journal, research was conducted in compliance with institutional guidelines, and any potential conflict of interest has been reported. Such disclosure will not preclude publication, but it is critical because of the potential of negative or positive bias. Potential conflicts of interest include funding sources for the reported study or financial interest in a test or product or with a company that publishes a test that is being investigated in the manuscript. In addition to signing this attestation, compliance with institutional research standards for animal or human research (including a statement that the research was completed in accordance with the Helsinki Declaration http://www.wma.net/e/policy/17-c_e.html) should be included in the methods section of the manuscript, and funding sources and other potential conflicts of interest should be included in the acknowledgements. See the Author Disclosure Form on website for specific details.

Manuscript Submission and Review

The *Journal of the International Neuropsychological Society* uses online submission and peer review. Paper submissions are not accepted. Authors who are not able to submit their manuscripts online are asked to contact the editorial office at: jins@unm.edu. The website address for submissions is: http://mc.manuscriptcentral.com/cup/jins, and complete instructions are provided on the website. Prior to online submission, please consult http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=mesh for 6 keywords or mesh terms that are different from words in the title. Accurate mesh terms will increase the probability that your manuscript will be identified in online searches. Please follow the instructions carefully to avoid delays. The menu will prompt the author to provide all necessary information, including the manuscript category, the corresponding author including phone number, fax number and e-mail address, and suggested reviewers.

The website will automatically acknowledge receipt of the manuscript and provide a manuscript reference number. The Editor-in-Chief will assign the manuscript for review to an Associate or Department Editor and at least two other reviewers. Every effort will be made to provide the author with a review within 6 to10 weeks of manuscript assignment. *Rapid Communications* will be reviewed within 6 weeks. If the Editor requests that revisions be made to a manuscript before publication, a maximum of 3 months will be allowed for preparation of the revision, except in unusual circumstances.

Manuscript Length

In order to increase the number of manuscripts that can be published in the *JINS*, please adhere to the following length requirements. Please provide a word count on the title page for abstract and for manuscript (not including abstract, tables, figures, or references). Manuscripts will be returned if they exceed length requirements.

Regular Research Articles: Maximum of 5,000 words (not including tables, figures, or references) and a 200 word abstract.

Brief Communications: Maximum of 2,500 words (not including abstract, tables, figures, or references) and a 150 word abstract, with a maximum of two tables or two figures, or one table and one figure, and 20 references.

Rapid Communications: Maximum of 1,000 words (not including abstract, tables, figures, or references) and a 150 word abstract, with a maximum of two tables or two figures, or one table and one figure, and 10 references.

Critical Reviews: Maximum of 7,000 words (not including abstract, tables, figures, or references) and a 200 word abstract. ***Critical Reviews* must be pre-approved by the Department Editor. Please e-mail your abstract to jins@unm.edu in order to receive prior approval.**

Dialogues: Maximum of 2,000 words for each segment (not including abstract, tables, figures, or references) and a 100 word abstract, with a maximum of two tables or two figures, or one table and one figure and 20 references. ***Dialogues* must be pre-approved by the Department Editor. Please e-mail your abstract to jins@unm.edu in order to receive prior approval.**

Symposia: Maximum of 5,000 words (not including abstract, tables, figures, or references) and a 200 word abstract. ***Symposia* must be pre-approved by the Department Editor. Please e-mail your abstract to jins@unm.edu in order to receive prior approval.**

Neurobehavioral Grand Rounds: Maximum of 5,000 words with an informative literature review (not including abstract, tables, figures, or references) and a 200 word abstract.

Letters to the Editor: Maximum of 500 words (not including table, figure, or references) with up to five references, one table, or one figure.

Book Reviews: Approximately 1,000 words.

Manuscript Preparation and Style

The entire manuscript should be typed double-spaced throughout using any word processing program. Unless otherwise specified, the guideline for preparation of manuscripts is the *Publication Manual of the American Psychological Association* (5th edition) except for references with 3 or more authors (see References section). This may be ordered from: APA Order Dept., 750 1st St. NE, Washington, DC 20002-4242, USA.

Pages should be numbered sequentially beginning with the Title Page. The Title Page should contain the full title of the manuscript, the full names and affiliations of all authors, a contact address with telephone and fax numbers and e-mail address, and the word count for abstract and for manuscript (excluding title page, abstract, references, tables, and figures). At the top right provide a short title of up to 45 characters preceded by the lead author's last name. Example: Smith-Memory in Parkinson's Disease. This running headline should be repeated at the top right of every following page.

The Abstract and Mesh terms (Keywords) on *page 2* should include a brief statement of the problem, the method, the key findings, and the conclusions. Six mesh or key words should be provided (see http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=mesh for list), and they should not duplicate words in the title.

The full text of the manuscript should begin on *page 3*. For scientific articles, including *Regular Research Articles*, *Brief Communications*, *Rapid Communications*, and *Symposia*, the format should include an Abstract, Introduction, Method, Results, and Discussion. This should be followed by References, Appendixes, Acknowledgments, Tables, Figures, and Figure Legends.

The use of abbreviations, except those that are widely used, is strongly discouraged. They should be used only if they contribute to better comprehension of the manuscript. Acronyms should be spelled out at first mention. Metric system (SI) units should be used.

Special Note Regarding Figures

Please upload your figure(s) in either a .doc or pdf. format. When uploading figures (color or black and white), they need only be a high enough resolution for the reviewers and editors to identify the information you are trying to convey. However, if your manuscript is accepted for publication, your figures must meet the following criteria:

High quality digital images (600 dpi or higher) should be provided in PDF, EPS, or TIFF formats. If a digital image is not available, please scan in the image. Figures should be numbered consecutively as they appear in the text. Any indication of features of special interest should also be included. Figures should be twice their intended final size and authors should do their best to construct figures with notation and data points of sufficient size to permit legible photo reduction to one column of a two-column format.

Color figures can be accepted. All color graphics must be formatted in CMYK and not in RGB, because 4-color separations cannot be done in RGB. However, the extra cost of printing these figures must be paid by the author, and the cost typically ranges from $700 to $1500 per figure.

Tables and figures should be numbered in Arabic numerals. The approximate position of each table and figure should be provided in the manuscript: [INSERT TABLE 1 HERE]. Tables and figures should be on separate pages. Tables should have short titles and all figure legends should be on separate pages.

References

References should be in American Psychological Association, 5th Edition, style (see the examples presented below).

Text references should be cited as follows: ". . . Given the critical role of the prefrontal cortex (PFC) in working memory (Cohen et al., 1997; Goldman-Rakic, 1987; Perlstein et al., 2003a, 2003b) . . ." with multiple references in alphabetical order. Another example is: "For example, Cohen et al. (1994, 1997), Braver et al. (1997), and Jonides and Smith (1997) demonstrated . . ." References cited in the text with three or more authors should state et al. (e.g., Smith et al.) even at first mention **(this deviates from the APA 5th Edition style)**. However, in the reference section all authors should be listed. Reference entries should be alphabetically listed in the reference section with all authors being cited. Examples of the APA reference style are as follows:

Scientific Article:

Haaland, K.Y., Price, L., & LaRue, A. (2003). What does the WMS-III tell us about memory changes with normal aging? *Journal of the International Neuropsychological Society, 9,* 89–96.

Book:

Lezak, M.D., Howieson, D.B., & Loring, D.W. (2004). *Neuropsychological Assessment.* New York: Oxford University Press

Book Chapter:

Knopman, D. & Selnes, O. (2003). Neuropsychology of Dementia. In K.M. Heilman & E.E. Valenstein (Ed.), *Clinical Neuropsychology.* New York: Oxford University Press.

Report at a Scientific Meeting:

Rothi, L.J.G. (2003, February). Use-dependent learning and neural plasticity: A revision of the pessimism surrounding neurorehabilitation. International Neuropsychological Society, Honolulu, Hawaii.

Manual, Diagnostic Scheme, etc.:

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.). Washington, DC: American Psychiatric Association Press.

Proofs

The publisher reserves the right to copyedit manuscripts. The corresponding author will receive PDFs for final proofreading. These should be checked and corrections returned within 2 days of receipt. The publisher reserves the right to charge authors for excessive corrections.

Offprints and PDF Files

The corresponding author will receive a free pdf. This pdf can also be mounted on the authors' web pages. Offprints must be ordered when page proofs are returned. The offprint order form with the price list will be sent with your PDF.

Appendix 3.1 Ethics Committee Approval Letter

South Glasgow and Clyde Local
Research Ethics Committee
Ross House
Hawkhead Road
Paisley
PA2 7BN
Telephone 0141 314 0309
Fax 0141 848 1414
www.show.scot.nhs.uk/achb/index.htm

NHS
Greater Glasgow and Clyde

Mr Steven Meldrum
Trainee Clinical Psychologist
Psychological Medicine
Gartnavel Royal Hospital
Glasgow
G12 0XH

Date 1 September 2006
Your Ref
Our Ref **06/S0702/43**

Enquiries to Evelyn Jackson
Extension 40309
Direct Line 0141 314 0309
Email Evelyn.Jackson@renver-pct.scot.nhs.uk

Dear Mr Meldrum

REC REF.	***06/S0702/43***
STUDY TITLE	***IS THERE A CENTRAL EXECUTIVE ATTENTIONAL DEFICIT IN MULTIPLE SCLEROSIS? EVIDENCE FROM SINGLE AND DIVIDED ATTENTION PARADIGMS***

Thank you for your letter of 21 August 2006, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chairman of South Glasgow and Clyde Local Research Ethics Committee.

Confirmation of Ethical Opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, as revised.

Ethical Review of Research Sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the research site(s) taking part in this study. The favourable opinion does not therefore apply to any site at present. I will write to you again as soon as one Local Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at sites requiring SSA.

Conditions of Approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Continued...../

1 September 2006

Letter to Mr S Meldrum, Southern General Hospital.....continued/

Approved Documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Application	-	-
Investigator CV	-	-
Protocol	-	27 March 2006
Advertisement	1	10 June 2006
Letter of invitation to participant	1	19 May 2006
GP/Consultant Information Sheets	1	19 May 2006
Participant Information Sheet	1	19 May 2006
Participant Information Sheet	2	21 August 2006
Participant Consent Form	2	21 August 2006
Participant Consent Form	1	19 May 2006
Response to Request for Further Information	-	21 August 2006
Supervisor's CV	-	-
Reply Form	1	19 May 2006

Research Governance Approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final research governance approval from the R&D Department for the relevant NHS care organisation.

Statement of Compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

Yours sincerely

Evelyn Jackson

Evelyn Jackson
Co-ordinator
South Glasgow and Clyde Local Research Ethics Committee

Copied to Sonia Whyte, R&D, Southern General Hospital

Encs.

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South Glasgow LREC

LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number:	06/S0702/43	**Issue number:**	1	**Date of issue:**	01 September 2006
Chief Investigator:	Mr Steven Meldrum				
Full title of study:	Is there a central executive attentional deficit in Multiple Sclerosis? Evidence from single and divided attention paradigms.				

This study was given a favourable ethical opinion by South Glasgow LREC on 31 August 2006. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	*Post*	*Research site*	*Site assessor*	*Date of favourable opinion for this site*	*Notes (1)*

Approved by the Chair on behalf of the REC:

Evelyn Jackson ..... *(Signature of Co-ordinator)* *Evelyn Jackson* (Name)

Appendix 3.2 Research and Development Approval letter

Acute Services Division

Diagnostics Directorate

NHS
Greater Glasgow and Clyde

Research & Development Office
5th Floor I.N.S. Southern General Hospital, 1345 Govan Road Glasgow G51 4TF

Professor D J Wyper: R&D Director
Mrs Sonia Whyte: R&D Co-ordinator
Dr Susan Graham: R&D Co-ordinator
Mrs Carolyn Stewart: R&D Officer

Tel: 0141 201 1890
Fax: 0141 201 2060
email: sonia.whyte@sgh.scot.nhs.uk

Our Ref: R060114/SW

7th September 2006

Mr. Steven Meldrum
Section of Psychological Medicine
Academic Centre
Gartnavel Royal Hospital
1055 Great Western Road
Glasgow
G12 0XH

Dear Steven,

Is there a central executive attentional deficit in multiple sclerosis? Evidence from single and divided attention paradigms.

I am writing to confirm that the South Glasgow University Hospital, Division of Greater Glasgow and Clyde Health Board ***is willing to undertake to role of Sponsor and that you have management approval for the above research study.***

Under the Scottish Executive's Research Governance Framework for Health and Community Care the Sponsor must ensure:

- The proposed work is consistent with the Research Governance Framework
- The research is appropriately managed and monitored
- Other stakeholder organisations are alerted of any significant developments that occur as the study progresses, whether in relation to safety of individuals or to scientific direction
- There is a clear statement provided concerning the arrangements for compensation in the event of non-negligent.

You are Chief Investigator and have agreed to ensure:

- The research has appropriate ethical and R&D management approval

- The researchers have the necessary expertise and access to the resources required to conduct the proposed research
- That any intellectual property (IP) arising from the research is identified and protected, where appropriate
- Arrangements are proposed for disseminating the research finding
- To advise R&D office of any changes i.e. to the protocol, recruitment numbers, staff.

I wish you every success with your study. Please don't hesitate to contact me should you require any further assistance.

Yours sincerely,

Sonia

Mrs. Sonia Whyte
Research & Development Co-ordinator

Appendix 3.3 Patient Information Sheet

South Glasgow
University Hospitals
Division

Southern General Hospital

1345 Govan Road
Glasgow G51 4TF
Telephone 014-201-1100
Fax 0141-201-2510
www.nhsgg.org.uk

NHS
Greater
Glasgow

Mr Steven Meldrum
Trainee Clinical Psychologist
The Sackler Research Centre
Institute of Neurological Sciences
1345 Govan Road
Glasgow G51 4TF

Section of Psychological Medicine, University of Glasgow

Institute of Neurological Sciences, Southern General Hospital, Glasgow

INFORMATION SHEET

INVESTIGATION OF ATTENTION DEFICITS IN MULTIPLE SCLEROSIS

Who is conducting the research?

The research is being carried out by Steven Meldrum, Trainee Clinical Psychologist and Professor Jonathan Evans from the Section of Psychological Medicine of the University of Glasgow, and Dr Colin O'Leary, Consultant MS Lead Neurologist of the West of Scotland Regional Multiple Sclerosis Service, Department of Neurology, Institute of Neurological Sciences, Southern General Hospital, Glasgow.

What is the research about?

The project is about investigating whether people with multiple sclerosis, in the early stages of the disease, have difficulties with different aspects of attention. When we talk of attention, we are referring to the ability to focus and concentrate when doing something and the ability to do more than one thing at the same time. Often, people with MS complain of having problems with attention, especially when they are doing more than one thing at the same time. Previous research with MS patients has found that problems with attention are quite common; however we do not yet fully understand the difficulties. We are looking to further understand what difficulties MS patients have with attention, especially in the early stages of the disease. To help us investigate this we have developed three simple computerised tasks that have been designed to assess different aspects of attention. We hope these tasks will allow us to further understand attention problems in MS patients. At this stage in our research we need patients in the early stages of MS to try out the three simple computerised tasks and then we will compare these results with results from a group of people who do not have MS or any other neurological problems. The number of participants to be recruited for this

study are 17 participants from the MS group and 17 participants from the control group that do not have neurological problems.

What does taking part involve?

We will invite you to come along to the Southern General Hospital, Glasgow where we will carry out the tests during one visit, which we expect to take no longer than 120 minutes.

First, we will do some simple paper and pencil tests of memory, concentration, language, mood, and vision. Then we will ask you to do the three simple computerised tasks of attention.

Does the research involve any medical examination or medication?

No.

What happens to the information?

The information from your test scores and the computerised attention tests are held in accordance with the Data Protection Act, which means that we keep it safely and cannot reveal it to other people – even the clinical team – without your permission. However, it may be beneficial to you if we put a summary of the test scores from the paper and pencil tests in your medical records. The reason for this is to do with the fact that it is better that some tests of memory and concentration are not repeated within a short space of time. If a member of the clinical team you are working with needed to do a test with you, then it would be helpful if the team member was aware of what tests you have done and the results. This may mean that you would not need to repeat the test again if you have done it already for this study. We will therefore ask your permission to place a written summary of the paper and pencil test scores in your medical records. We will not do this without your permission.

If we publish any findings from the study, this will be in the form where your results are combined with those of many other people and *average* scores, which are anonymised, are presented. We take very special care not to publish any details that could lead an individual to be identified. If you would like to see an example of the form in which results are published, please just ask a member of the study team.

If I don't want to take part in the study?

Whether or not to take part is entirely up to you. Whilst our research relies on the help of volunteers we quite understand that there may be many reasons not to take part. You do not need to give a reason and we completely respect that decision. This project is completely separate from any clinical services you may be receiving and your decision has no effect on your access to these services.

If I agree to take part and then later change my mind?

You are under no obligation and can withdraw from the study at any stage without having to give a reason.

Will taking part have any advantages for me?

Our research is experimental and designed to further understand what attention problems people in the early stages of MS might have. Therefore it is unlikely, and you should assume, that taking part in this research project will have no specific beneficial effects for you. We will be happy to summarise the results of the various tests for you if you want us to do this.

Who has reviewed the study?

This study has been reviewed and passed by the South Glasgow Research Ethics Committee (REC reference number: 06/S0702/43).

If I have any further questions?

We will give you a copy of this information sheet, letter of invitation, and the signed consent form (Version 2, dated 21/08/06) to keep. However, if you would like more information before deciding whether or not to take part, then please do not hesitate to contact a member of the research team.

Who should I contact?

The research team are:

Steven Meldrum, Trainee Clinical Psychologist, Section of Psychological Medicine, Gartnavel Royal Hospital, Glasgow, G12 0XH.
Telephone: 0775 1080098
Email: stevepsychologist@yahoo.co.uk

Professor Jonathan Evans, Professor of Applied Neuropsychology, Section of Psychological Medicine, Gartnavel Royal Hospital, Glasgow, G12 0XH
Telephone: 0141 211 3978
Email: jje2k@clinmed.gla.c.uk

Dr Colin O'Leary (Lead Clinician), West of Scotland Regional Multiple Sclerosis Service, Department of Neurology, Institute of Neurological Sciences, Southern General Hospital, 1345 Govan Road, Glasgow G51 4TF
Telephone: 0141 201 1100
Email: cpol1j@clinmed.gla.ac.uk

If I have a complaint about any aspect of this study?

If you are unhappy with any aspect of your participation in the project, please first contact Steven Meldrum, who is the principle investigator for the project. Should any complaint not be resolved satisfactorily, you can contact the following people: Professor Jonathan Evans, Dr Colin O'Leary (Lead Clinician), or Sonia Whyte, Southern General Hospital, Research and Development Dept., 0141 201 1890.

Appendix 3.4 **Patient Consent Form**

South Glasgow
University Hospitals
Division

Southern General Hospital

1345 Govan Road
Glasgow G51 4TF

Telephone 014-201-1100
Fax 0141-201-2510
www.nhsgg.org.uk

NHS
Greater
Glasgow

Mr Steven Meldrum
Trainee Clinical Psychologist
The Sackler Research Centre
Institute of Neurological Sciences
1345 Govan Road
Glasgow G51 4TF

Section of Psychological Medicine, University of Glasgow

Institute of Neurological Sciences, Southern General Hospital, Glasgow

INVESTIGATION OF ATTENTION DEFICITS IN MULTIPLE SCLEROSIS

CONSENT FORM

Please initial box

I confirm that I have read and understand the information sheet (Version 2, dated 21/08/06) for the above study and have had the opportunity to ask questions ☐

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 understand that sections of my medical notes may be looked at by the research team where it is relevant to my taking part in the research. I give my permission for the research team to have access to my records. ☐

I give my permission for a summary of scores from standard neuropsychological tests used in this study to be placed in my medical records. ☐

I give my permission for my GP to be informed that I am taking part in the study. ☐

I agree to take part in the study. ☐

_____ _____ _____

Name of participant **Date** **Signature**

Appendix 3.5 GP Information Letter

South Glasgow
University Hospitals
Division

Southern General Hospital

1345 Govan Road
Glasgow G51 4TF
Telephone 014-201-1100
Fax 0141-201-2510
www.nhsgg.org.uk

NHS
Greater
Glasgow

Mr Steven Meldrum
Trainee Clinical Psychologist
The Sackler Research Centre
Institute of Neurological Sciences
1345 Govan Road
Glasgow G51 4TF

Section of Psychological Medicine, University of Glasgow

Institute of Neurological Sciences, Southern General Hospital, Glasgow

INVESTIGATION OF ATTENTION DEFICITS IN MULTIPLE SCLEROSIS

GP Information Sheet

Dear Dr.....

PATIENT DETAILS:.....

I am writing to inform you that the above named patient is taking part in a study investigating attention deficits in multiple sclerosis.

Deficits in attention are a common cognitive finding in patients with multiple sclerosis, even in the early stages of the disease. In particular, the ability to divide attention between two competing tasks at the same time is problematic in multiple sclerosis. For example, previous research has investigated divided attention in MS using dual tasking experiments, where patients perform two tasks concurrently, and findings suggest that compared to healthy controls, MS patients perform less well.

The present study aims to investigate and further understand attention problems that patients with MS have. The study involves the development of three computerised tests of attention that focus on visual, auditory, and bimodal divided attention which we expect to be sensitive to attention deficits in MS. Performance results on the tests from the MS group will be compared with an age and education matched control group.

Your patient has agreed to take part in this study, which has approval from the Greater Glasgow and Clyde Health Board, South Glasgow University Hospitals Division Ethics Committee (Approval reference: 06/S0702/43). The study will involve your patient attending the Southern General Hospital Glasgow for a session of about 120 minutes in which the computerised attention tests and a small

number of other standard neuropsychological tests will be administered. It is not anticipated that there will be any adverse effects of taking part in this study.

Should you have any questions about the study please contact a member of the research team:

Steven Meldrum, Trainee Clinical Psychologist, Section of Psychological Medicine, Gartnavel Royal Hospital, Glasgow, G12 0XH.
Telephone: 0141 211 3927
Email: stevepsychologist@yahoo.co.uk

Professor Jonathon Evans, Professor of Applied Neuropsychology, Section of Psychological Medicine, Gartnavel Royal Hospital, Glasgow, G12 0XH
Telephone: 0141 211 3978
Email: jje2k@clinmed.gla.c.uk

Dr Colin O'Leary (Lead Clinician), West of Scotland Regional Multiple Sclerosis Service, Department of Neurology, Institute of Neurological Sciences, Southern General Hospital, 1345 Govan Road, Glasgow G51 4TF
Telephone: 0141 201 1100
Email: cpol1j@clinmed.gla.ac.uk

Appendix 3.6 Guidelines for submission to Journal of the International Neuropsychological Society

JOURNAL OF THE INTERNATIONAL NEUROPSYCHOLOGICAL SOCIETY

Instructions for Contributors

Aims and Scope:

The *Journal of the International Neuropsychological Society* welcomes original, creative, high quality research papers covering all areas of neuropsychology. The focus of articles may be primarily experimental, more applied or clinical. Contributions will broadly reflect the interest of all areas of neuropsychology, including but not limited to: development of cognitive processes, brain-behavior relationships, adult and pediatric neuropsychology, neurobehavioral syndromes, such as aphasia or apraxia, and the interfaces of neuropsychology with related areas such as behavioral neurology, neuropsychiatry, and cognitive neuroscience. Papers that utilize behavioral, neuroimaging, and electrophysiological measures are appropriate. Book reviews will also be published.

To assure maximum flexibility and to promote diverse mechanisms of scholarly communication, the following formats are available in addition to *Regular Research Articles: Brief Communications* are shorter research articles; *Rapid Communications* are intended for "fast breaking" new work, that does not yet justify a full length article, and which are put on a fast review track; *Neurobehavioral Grand Rounds* are unique case studies, which are published in tandem with an introduction by an expert in the field to put the case into a more global perspective; *Critical Reviews* are thoughtful considerations of topics of importance to neuropsychology, including associated areas, such as functional brain imaging, neuroepidemiology, and ethical issues; *Dialogues* provide a forum for publishing two distinct positions on controversial issues in a point-counterpoint form; *Symposia* consist of several research articles that are thematically linked; *Letters to the Editor* respond to recent articles in the *Journal of the International Neuropsychological Society;* and *Book Reviews*.

Critical Reviews, *Dialogues*, and *Symposia* may be invited by the appropriate Department Editor or proposed by individual authors. Such proposals should be discussed with the Editor-in-Chief or the Department Editor before submission. *Book Reviews* are invited by the Book Review Editor.

Originality and Copyright

To be considered for publication in the *Journal of the International Neuropsychological Society*, a manuscript cannot have been published previously, nor can it be under review for publication elsewhere. Papers with multiple authors are reviewed with the assumption that all authors have approved the submitted manuscript and concur with its submission to the *Journal of the International Neuropsychological Society*. **A Copyright Transfer Agreement**, with certain specified rights reserved by the author, must be signed and returned to the Editor by the corresponding author of accepted manuscripts, prior to publication. This is necessary for the wide distribution of research findings, and the protection of both author and the society under copyright law.

Disclosure Form

An Author Disclosure Form must be signed by the corresponding author at the time the manuscript is submitted. This form includes an attestation that the manuscript is original and not under review in another journal, research was conducted in compliance with institutional guidelines, and any potential conflict of interest has been reported. Such disclosure will not preclude publication, but it is critical because of the potential of negative or positive bias. Potential conflicts of interest include funding sources for the reported study or financial interest in a test or product or with a company that publishes a test that is being investigated in the manuscript. In addition to signing this attestation, compliance with institutional research standards for animal or human research (including a statement that the research was completed in accordance with the Helsinki Declaration http://www.wma.net/e/policy/17-c_e.html) should be included in the methods section of the manuscript, and funding sources and other potential conflicts of interest should be included in the acknowledgements. See the Author Disclosure Form on website for specific details.

Manuscript Submission and Review

The *Journal of the International Neuropsychological Society* uses online submission and peer review. Paper submissions are not accepted. Authors who are not able to submit their manuscripts online are asked to contact the editorial office at: jins@unm.edu. The website address for submissions is: http://mc.manuscriptcentral.com/cup/jins, and complete instructions are provided on the website. Prior to online submission, please consult http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=mesh for 6 keywords or mesh terms that are different from words in the title. Accurate mesh terms will increase the probability that your manuscript will be identified in online searches. Please follow the instructions carefully to avoid delays. The menu will prompt the author to provide all necessary information, including the manuscript category, the corresponding author including phone number, fax number and e-mail address, and suggested reviewers.

The website will automatically acknowledge receipt of the manuscript and provide a manuscript reference number. The Editor-in-Chief will assign the manuscript for review to an Associate or Department Editor and at least two other reviewers. Every effort will be made to provide the author with a review within 6 to10 weeks of manuscript assignment. *Rapid Communications* will be reviewed within 6 weeks. If the Editor requests that revisions be made to a manuscript before publication, a maximum of 3 months will be allowed for preparation of the revision, except in unusual circumstances.

Manuscript Length

In order to increase the number of manuscripts that can be published in the *JINS*, please adhere to the following length requirements. Please provide a word count on the title page for abstract and for manuscript (not including abstract, tables, figures, or references). Manuscripts will be returned if they exceed length requirements.

Regular Research Articles: Maximum of 5,000 words (not including tables, figures, or references) and a 200 word abstract.

Brief Communications: Maximum of 2,500 words (not including abstract, tables, figures, or references) and a 150 word abstract, with a maximum of two tables or two figures, or one table and one figure, and 20 references.

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Book Chapter:

Knopman, D. & Selnes, O. (2003). Neuropsychology of Dementia. In K.M. Heilman & E.E. Valenstein (Ed.), *Clinical Neuropsychology.* New York: Oxford University Press.

Report at a Scientific Meeting:

Rothi, L.J.G. (2003, February). Use-dependent learning and neural plasticity: A revision of the pessimism surrounding neurorehabilitation. International Neuropsychological Society, Honolulu, Hawaii.

Manual, Diagnostic Scheme, etc.:

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.). Washington, DC: American Psychiatric Association Press.

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