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# O FOTOTEST NO RASTREIO NEUROCOGNITIVO NA ESCLEROSE MÚLTIPLA

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# Introdução

O presente estudo insere-se no Seminário de Investigação para a obtenção de grau Mestre em Neuropsicologia Clínica no Instituto Superior de Ciências da Saúde - Norte. Foi realizado sob a orientação do Professor Doutor Bruno Peixoto, no Centro Hospitalar do Alto Ave.

Centra-se no estudo da validade do Fototest (FT) na avaliação neurocognitiva de doentes com Esclerose Múltipla (EM), comparativamente com um teste de screening mais extenso com validade comprovada nesta doença, o *Montreal Cognitive Assessment* (MoCa). O FT consiste num teste de avaliação neurocognitiva breve, que tem revelado boas caraterísticas psicométricas noutras populações clínicas. Consideramos pertinente a utilização do FT na EM, uma vez que avalia fluência verbal e memória episódica, dois dos domínios cognitivos mais comumente afetados nesta patologia.

O resumo foi submetido ao I Simpósio Europeu de Neuropsicologia, tendo sido selecionado para apresentação na forma de poster e ao *3rd International Porto Congress of Multiple Sclerosis*.

O artigo submetido à revista *Multiple Sclerosis and Related Disorders* está organizado em seis partes fundamentais, segundo as normas da mesma. A primeira parte é o resumo da investigação. A segunda parte consiste na revisão bibliográfica que incide nas principais alterações cognitivas que surgem na EM, nas potencialidades do FT, seguidas dos objectivos orientadores do estudo. A terceira parte compreende a descrição da metodologia utilizada, procedendo-se a uma caraterização da amostra, instrumentos e procedimentos adotados. Na quarta parte apresentam-se os resultados, caraterísticas clínicas dos doentes com EM, abordagem comparativa com os resultados obtidos pelos controlos no FT e no MoCa e caraterísticas psicométricas do FT. De seguida, surge a discussão, enquadrando-se os resultados obtidos nos objetivos orientadores da investigação. Por fim, na conclusão destacam-se os principais contributos deste estudo, respetivas implicações e limitações.

**Índice**

## Resumo

Background: A Esclerose Múltipla (EM) é das doenças neurológicas mais comuns. A disfunção cognitiva consiste num marcador clínico da EM, cerca de metade dos pacientes apresentam comprometimento cognitivo.

Objetivos: O Fototest (FT) é um teste breve, sensível, específico e com boa relação custo-eficácia na deteção de deterioração cognitiva. Pretendemos testar a validade do FT como um instrumento de screening neurocognitivo na EM.

Métodos: O estudo envolveu uma amostra de 30 doentes com diferentes tipos de EM de uma clínica de tratamento ambulatório e 19 participantes saudáveis. Em conjunto com o FT, foram aplicados o *Montreal Cognitive Assessment* (MoCA), o Índice de Barthel (IB), a *Expanded Disability Status Scale* (EDSS) e a Escala de Severidade de Fadiga (FSS).

Resultados: O grupo EM obteve resultados significativamente inferiores em todos os domínios do FT, excepto na tarefa de nomeação. O FT apresenta boa validade concorrente com o MoCa. Na comparação direta com o MoCa, o FT revelou uma área sob a curva superior e níveis de sensibilidade e especificidade para os défices cognitivos na EM superiores. Ao ponto de corte de 31 no FT correspondem valores de sensibilidade de 100% e especificidade de 76,7%.

Conclusão: O FT é um teste válido, específico, sensível e breve, não dependente das funções sensoriomotoras. Pode ser uma opção para o *screening* neurocognitivo na EM, especialmente na identificação de casos para posterior avaliação neuropsicológica e intervenção.



**Palavras-chave:** Esclerose Múltipla, Fototest, *Montreal Cognitive Assessment*, *Expanded Disability Status Scale*, Escala de Severidade de Fadiga

**Abstract**

Background: Multiple Sclerosis (MS) is one of the most common neurological disorders. Cognitive dysfunction is considered a clinical marker of MS, approximately half of patients with MS have cognitive impairment.

Objective: The Phototest (PT) is a brief cognitive test, with great diagnostic sensitive, accuracy and cost-effectiveness in detection of cognitive deterioration. Our aim is to test the utility of PT as a neurocognitive screening instrument for MS.

Methods: The study enrolled 30 patients with different types of MS from an outpatient clinic and 19 healthy participants. In complement to PT, the Montreal Cognitive Assessment (MoCA), Barthel Index (BI), Expanded Disability Status Scale (EDSS), Fatigue Severity Scale (FSS), were administered.

Results: The MS group obtained significantly lower results in all domains of PT, except on the naming task. The PT revealed good concurrent validity with MoCA. In direct comparison to MoCA, PT revealed a higher area under the curve and higher levels of sensitivity and specificity for MS neurocognive impairments. A cut-off score of 31 on PT showed a sensitivity of 100% and a specificity of 76.7%.

Conclusion: PT is a valid, specific, sensitive and brief test, not dependent on sensoriomotor functions. It could be an option for neurocognitive screening in MS, especially in identifying cases for further neuropsychological assessment and intervention.

**Keywords:** Multiple Sclerosis, Fototest, Montreal Cognitive Assessment, Expanded Disability Status Scale, Fatigue Severity Scale

## 1. Introdução

A Esclerose Múltipla (EM) é das doenças neurológicas mais comuns (World Health Organization [WHO], 2006). A EM é mais frequente em locais distantes do equador em ambos os hemisférios e mais comum no sexo feminino do que no sexo masculino, o que sugere a interação entre fatores genéticos e ambientais. Nos países ocidentais, constitui a causa de incapacidade mais frequente nos adultos jovens (WHO, 2006). É mais frequentemente diagnosticada em indivíduos entre os 20 e os 40 anos de idade, quando os pacientes estão economicamente ativos representando, assim, custos diretos e indiretos para o sistema nacional de saúde. De acordo com dados recentes, estima-se que haja cerca de 5000 pessoas com EM em Portugal (Machado et al., 2010).

Os padrões típicos de progressão da doença são: recidivante/remitente, primária progressiva e secundária progressiva (WHO, 2006). A combinação de sintomas é variável, resultando em diferentes apresentações da doença (Freeman et al., 2008). Os principais sintomas incluem: a fadiga e a disfunção cognitiva (WHO, 2008; Ko, 1999). A disfunção cognitiva é considerada um marcador clínico da EM (Nocentini et al., 2006) e abrange todas as fases da doença e tipos de progressão clínica, resultando em limitações no trabalho e na vida social, independentemente do grau de incapacidade física (Amato et al., 2006). O comprometimento cognitivo afeta até 65% dos pacientes, pode ocorrer desde os estágios iniciais da doença e tende a agravar-se ao longo do tempo (Hulst et al., 2014; Amato et al., 2006; Achiron et al., 2005). No entanto, devido aos custos, consumo de tempo e focalização nas deficiências físicas, estas alterações não são avaliadas por rotina (Messinis et al., 2010).

O funcionamento intelectual geral encontra-se preservado na maioria dos pacientes (Drew et al., 2008), apesar do comprometimento significativo na inteligência fluida (Thornton & Defreitas, 2009). A velocidade de processamento de informação visual e auditiva e a fluência verbal são as áreas cognitivas mais precocemente afetadas (Nocentini et al., 2006; Achiron et al., 2005). A diminuição da velocidade de processamento representa o sinal mais proeminente e comum na EM e está intimamente relacionada com a severidade da doença (Hankomäki et al., 2014; Van Schependom et

al., 2014a). A diminuição da velocidade de processamento também prejudica a codificação da memória de trabalho (Demaree et al., 1999; Lengenfelder et al., 2006). Os défices na fluência verbal semântica e fonologia são também comuns entre os pacientes com EM (Henry & Beatty, 2006). A fluência verbal parece estar comprometida na fase inicial da EM recidivante/remitente e este défice aumenta com a duração da EM (Brissart et al., 2013). As tarefas de fluência verbal e velocidade de processamento podem estar entre as medidas neuropsicológicas mais sensíveis aos défices cognitivos na EM (Henry & Beatty, 2006).

Com a progressão da doença, os défices na memória, particularmente na codificação, organização semântica (Drake et al., 2006), evocação e recordação tardia (Achiron et al., 2005; Zakzanis, 2000), tornam-se mais evidentes. Nas tarefas de recordação tardia os pacientes revelam erros de confabulação, consistentes com a disfunção do lobo frontal (Drake et al., 2006). Para além disso, apresentam défices na memória de trabalho (Nocentini et al., 2006; Lengenfelder et al., 2006, Zakzanis, 2000), na memória de trabalho espacial (Foong et al., 1997), na memória verbal e visual a longo prazo (Andrade et al., 1999), na memória não verbal (Grant et al., 1984), na memória visuo-espacial de curto e de longo-prazo (Piras et al., 2003) e na memória auto-biográfica (Thornton & Defreitas, 2009).

No funcionamento executivo, verifica-se comprometimento da capacidade de resolução de problemas (Beatty &Monson, 1996; Drew et al., 2008; Piras et al., 2003), do raciocínio abstrato (Piras et al., 2003), do planeamento, da organização, da mudança de regra, da inibição, da fluência verbal (Drew et al., 2008; Foong et al., 1997), das tarefas de Stroop, da estimativa cognitiva, do *span* espacial e da utilização de estratégias (Foong et al., 1997). Os défices na atenção dividida, na atenção sustentada (McCarthy et al., 2005) e na atenção focalizada (Thornton & Defreitas, 2009) também são frequentes.

As capacidades visuoconstrutivas e visuopercetivas também estão afetadas (Vleugels et al., 2000), particularmente na discriminação da cor e de perceção da ilusão de *Muller-Lyer*, assim

como, na integração visuoespacial, discriminação visual e nas tarefas complexas de reconhecimento facial (Thornton & Defreitas, 2009).

Os défices na linguagem não são comuns (Thornton & Defreitas, 2009), contudo alguns autores apontam para dificuldades de nomeação (Drake et al., 2002), défices na organização linguística, mecanismos de recuperação e manipulação semântica e de processamento (Barwood and Murdoch, 2013).

A avaliação cognitiva dos pacientes com EM é o primeiro passo para a deteção precoce do comprometimento neurocognitivo e para a implementação de medidas terapêuticas de modo a prevenir o declínio e reduzir o impacto dos défices na vida dos pacientes. No entanto, esta avaliação não é realizada por rotina pela falta de ferramentas sensíveis, simples, fáceis de administrar e interpretar e com uma boa relação custo-eficácia (Patti, 2009).

O FT (www.fototest.es) é um teste cognitivo breve (<3 minutos), fácil de administrar e que avalia vários domínios cognitivos (linguagem, memória episódica e fluência verbal). Revelou-se sensível, específico e com boa relação custo-eficácia na deteção da deterioração cognitiva em contexto de Défice Cognitivo Ligeiro (Sánchez et al., 2007; Carnero-Pardo et al., 2007; Carnero-Pardo et al, 2011a, 2011b). Considerando os custos baseados em preços públicos e contas hospitalares, os custos envolvidos com o uso do FT são consideravelmente inferiores em comparação com outros testes de rastreio (Carnero-Pardo et al, 2011b.; Vilar et al., 2007). Dado que não é necessária leitura e não tem tarefas de papel e lápis, este teste é adequado para uso com analfabetos ou pessoas com um baixo nível educacional (Carnero-Pardo et al, 2011a).

Dadas as caraterísticas clínicas da EM, pretendemos testar a adequação do FT como um instrumento de screening cognitivo no contexto de EM. Pelo que, iremos determinar a validade discriminativa, a sensibilidade e especificidade do FT, bem como a sua validade concorrente e relação com variáveis clínicas.

## 2. Método

### 2.1 Participantes

A amostra está organizada em dois grupos: um grupo clínico constituído por 30 indivíduos (19 mulheres e 11 homens) com diagnóstico de EM e um grupo de controlo constituído por 19 indivíduos saudáveis (14 mulheres e 5 homens) (tabela 1). Os pacientes foram recrutados na consulta externa de neurologia do Centro Hospitalar do Alto Ave, e os indivíduos do grupo de controlo são dadores de sangue.

Indivíduos com história prévia de doenças neuropsiquiátricas ou sistémicas suscetíveis de interferir diretamente no funcionamento cognitivo foram excluídos. O abuso de álcool e drogas, o analfabetismo e alterações sensoriopercetivas não corrigidas constituíram, igualmente, critérios de exclusão.

Para garantir que o grupo de controlo se encontrava incólume em termos cognitivos, indivíduos com resultados iguais ou inferiores a um desvio padrão no MoCa foram excluídos.

Os grupos não diferem entre si no que diz respeito à idade ( $t = -2.013$; $p = .485$ ), sexo ( $\chi 2 = .567$; $p = .541$ ) e escolaridade ( $t = 1.016$ ; $p = .504$ ).

### 2.2 Instrumentos

#### 2.2.1 Fototest

O FT é um teste cognitivo breve, fácil de administrar que compreende três partes: uma tarefa de nomeação com seis fotografias a cores de objetos comuns; uma tarefa de fluência verbal categórica, em que os participantes devem evocar nomes masculinos e femininos; e uma tarefa de recordação livre e facilitada dos seis objetos usados na tarefa de nomeação. Este teste foi desenvolvido em Espanha e tem provado uma grande precisão e eficácia no contexto de comprometimento cognitivo e demência, mesmo quando comparado com testes mais tradicionais de *screening*, como o *Mini Mental State Examination* (Carnero-Pardo & Montoro-Ríos, 2004; Carnero-Pardo et al.,

2011a; Sánchez et al., 2007) ou o *Memory Alteration Test* (Carnero-Pardo et al., 2011b). Foi demonstrado que os pontos de corte de 26 e 28 oferecem uma validade discriminativa satisfatória para demência e comprometimento cognitivo, respetivamente (Carnero-Pardo et al., 2007) e também tem uma boa confiabilidade teste-reteste e inter-observadores (Carnero-Pardo et al., 2011c). Este teste tem dados normativos e algumas caraterísticas psicométricas para a população portuguesa (Dias et al., S/D).

### *2.2.2 Montreal Cognitive Assessment*

O *Montreal Cognitive Assessment* (MOCA) consiste num teste de *screening* cognitivo que avalia vários domínios cognitivos, como: funções executivas através de uma forma abreviada do *trail making test* parte B (TMT B); capacidades visuoespaciais pela cópia de cubo tridimensional (Cubo) e tarefa de desenho do relógio (Relógio); linguagem avaliada através de uma tarefa de nomeação de três animais (Nomeação), repetição de duas frases complexas (Frases) e uma tarefa de fluência verbal fonética (Fluência Verbal); atenção e concentração, avaliadas através da repetição direta e indireta de sequências numéricas (Dígitos), de cancelamento (Cancelamento) e de uma tarefa de subtração em série (Subtração); raciocínio abstrato por uma tarefa de similaridades (Similaridades); memória através da aprendizagem e evocação diferida de 5 palavras (Evocação Diferida); orientação temporal e espacial são avaliadas através de 6 questões (Orientação). Este teste foi utilizado porque apresenta elevada sensibilidade para comprometimento cognitivo na EM (Aksoy et al., 2013; Dagenais et al, 2013; Kaur et al, 2013), tornando-se um bom instrumento para determinar a validade concorrente do FT. O MoCa também foi usado para garantir a normalidade cognitiva dos indivíduos do grupo de controlo.

### 2.2.3 Escala de Severidade da Fadiga

A Escala de Severidade da Fadiga (FSS) é uma escala de auto-relato que avalia a perceção dos níveis de fadiga na EM no funcionamento físico, exercício, trabalho, família ou vida social. Apresenta boas qualidades psicométricas para a avaliação da perceção de fadiga, tendo revelado uma ótima validade de constructo (Pereira & Duarte, 2010). A FSS foi aplicada para caraterizar a amostra clinical e correlacionar com os resultados no FT.

### 2.2.4 Índice de Barthel

O Índice de Barthel (IB) avalia 10 atividades: comer, a higiene pessoal, o uso dos sanitários, o tomar banho, o vestir e despir, o controlo dos esfíncteres, o deambular, a transferência da cadeira para a cama e, por fim, o subir e descer escadas. Este instrumento reúne boas qualidades psicométricas para a avaliação da funcionalidade nas atividades da vida diária em pacientes portugueses (Araújo et al., 2007).

### 2.2.5 *Expanded Disability Status Scale*

A *Expanded Disability Status Scale* (EDSS) é a escala mais conhecida e amplamente utilizada na quantificação do grau de incapacidade na EM (Sharrack et al., 1999). Avalia 8 sistemas funcionais: piramidal, cerebelar, tronco cerebral, sistema sensorial, intestino e bexiga, visual e cerebral (Kurtzke, 1970, 1983). Os resultados obtidos na EDSS variam entre 0 (normal) a 10 (morte devido à EM) (Kurtzke, 1970, 1983). Revela boa fidelidade inter e intra-observadores e boa validade facial com outras escalas de avaliação da incapacidade (Sharrack et al., 1999). A EDSS foi utilizada para determinar o grau de incapacidade neurológica do grupo clínico e para correlacionar com os resultados no FT.

### 2.3 Procedimentos

O estudo teve o parecer favorável da Comissão de Ética do Centro Hospitalar do Alto Ave e todos os participantes deram o seu Consentimento Informado. Todos os indivíduos foram avaliados com o FT e o MoCa. O IB, a FSS e a EDSS foram aplicados apenas ao grupo clínico. A avaliação neuropsicológica foi efetuada em sala fechada e durou aproximadamente catorze minutos.

### 2.4 Análise de dados

Para a análise dos resultados do estudo servimo-nos do software estatístico SPSS, versão 21.0.

Utilizamos medidas de tendência central e desvio para analisar as características da amostra e dos resultados obtidos. A comparação do desempenho nos testes entre grupos, foi efetuada através do teste *U* de *Mann-Whitney*. A sensibilidade e a especificidade do FT, foram determinadas através da *Receiver Operating Curve* (ROC). A validade concorrente entre o FT e o MoCa, foi calculada através do coeficiente de correlação de *Spearman*.

Um valor de $p<.05$ foi considerado estatisticamente significativo.

## 3. Resultados

### 3.1. Caraterísticas Clínicas

As caraterísticas clínicas do grupo EM são apresentadas na Tabela 2. A maioria da amostra é composta por pacientes com EM recidivante-remitente. Todos os pacientes recebem medicação para a EM. De um modo geral, a amostra revela um nível de incapacidade moderado (EDSS) e está funcional para as atividades da vida diária, apesar da perceção de níveis moderados de fadiga.

### 3.2. Comparações entre pacientes com EM e Controlos

Os pacientes com EM revelaram um desempenho significativamente inferior em ambos os testes neurocognitivos e na maioria das tarefas. As tarefas de nomeação do FT e do MoCa, bem como as tarefas de dígitos, cancelamento, repetição de frases, similaridades e orientação do MoCa não mostraram diferenças significativas entre os grupos (tabela 3).

### 3.3. Resultados da análise da sensibilidade e especificidade do FT

Os resultados no FT correlacionam-se positivamente com os obtidos no MoCa ($\rho = 0.589$; $p = .000$). O desempenho no MoCa correlaciona-se positivamente com os resultados no IB ($\rho = 0.362$; $p = .050$). Nenhum dos testes neurocognitivos mostrou qualquer correlação quer com a FSS ou a EDSS. O mesmo foi observado em relação ao número de surtos e duração da doença.

O FT apresenta uma área sob a curva de .826 (S.E. = .57; p = .000), superior à área sob a curva gerada pelo MoCa ( AUC= .81 ; S.E. = .061 ; p = .000 ), para distinguir pacientes de controlos.

De acordo com o ponto de corte de 31 pontos, o FT tem uma sensibilidade de 100% e uma especificidade de 76,7%. O ponto de corte de 24 pontos no MoCa representa uma sensibilidade de 89,5% e a uma especificidade de 36,7%. Os pontos de corte representam dois desvios padrão de

acordo com os estudos de normalização portuguesa destes dois testes, baseados na média de idades e anos de escolaridade da nossa amostra.

## 4. Discussão

O FT provou ser um instrumento sensível e específico para avaliar o funcionamento neurocognitivo geral na EM. Embora a tarefa de nomeação não permita distinguir os dois grupos, a pontuação total do teste revelou valores de sensibilidade e especificidade superiores, quando comparados com o MoCa. Contudo, o desempenho no FT não mostra relação com a fadiga, a funcionalidade nas atividades da vida diária, a incapacidade e a duração da doença.

Os nossos resultados revelaram uma boa validade concorrente com o MoCa, um teste mais extenso para o *screening* neurocognitivo na EM (Aksoy et al., 2013). Talvez a existência de duas tarefas de fluência verbal no FT tenham contribuído para este achado. Como referido anteriormente, a fluência verbal é uma das funções neurocognitivas mais precocemente afetadas na EM (Brissart et al., 2013; Henry & Beatty, 2006). Para além disso, a transição entre duas tarefas de fluência verbal no FT requer controlo inibitório verbal, bem como mudança de regra. Assim, as tarefas de fluência verbal no FT indiretamente englobam componentes executivos implicados na EM (Drew et al., 2008; Foong et al., 1997). Os componentes executivos implícitos na fluência verbal são fortemente influenciados pela velocidade de processamento (Leavitt et al., 2014), outro domínio cognitivo comumente afetado na EM (Hankomäki et al., 2014; Van Schependom et al., 2014a).

A velocidade de processamento e as funções executivas constituem os principais preditores da *performance* na memória episódica (Barthelemy et al., 2014). Esta observação pode explicar o facto de os pacientes com EM recordarem menos objetos livremente e de terem recorrido à recordação facilitada com mais frequência do que os controlos.

As alterações ao nível da linguagem não são comuns na EM (Thornton & Defreitas, 2009), justificando, assim, a ausência de diferenças entre os grupos na tarefa de nomeação. As dificuldades de nomeação são mais comuns na EM progressiva (Beatty et al., 1988, 1989) e a nossa amostra foi maioritariamente composta por pacientes com EM recidivante-remitente.

O screening cognitivo na EM é condicionado pelo facto de apenas uma percentagem de doentes apresentarem défices cognitivos e estes serem muito diversos (Rao, 1990). A utilização do FT pode obviar estes problemas no *screening* cognitivo na EM, uma vez que avalia dois dos domínios mais comumente afetados: a fluência verbal e a memória episódica (Rao, 1990; Fisher, 2001; Sepulcre et al. 2011).

O FT revela níveis de sensibilidade e especificidade superiores aos do MoCa, talvez devido à inclusão de várias tarefas que não demonstraram diferenças significativas entre os grupos.

O FT apresenta um valor de sensibilidade superior à maioria dos testes de *screening* cognitivo recomendados por Rogers e Panegyres (2007) para a EM: o *Symbol Digits Modalities Test* (82% e 91%) (Parmenter et al., 2007), o PASAT (74%) (Rosti-Otajärvi, 2008), o Teste do Desenho do Relógio (92%) (Mohammad-Taghi & Fakhrossadat, 2014) e o *Multiple Sclerosis Neuropsychological Screening Questionnaire* (83%) (Benedict et al., 2003).

Relativamente à especificidade, o FT tem níveis mais elevados quando comparados com vários testes de triagem na EM. Bons exemplos são o *Paced Auditory Serial Addition Task* (PASAT), com uma especificidade de 65% (Rosti-Otajärvi, 2008) e o *Symbol Digits Modalities Test*, com uma especificidade de 61% (Van Schependon et al., 2014b). No entanto, quando comparado com o Teste do Desenho do Relógio (especificidade de 89%) (Mohammad-Taghi & Fakhrossadat, 2014), o FT mostra menor especificidade, provavelmente porque a tarefa de desenho do relógio requere funções adicionais, como organização visuoespacial, planeamento e capacidade de abstração, intimamente relacionadas com o lobo frontal (Benedict et al., 2002).

Embora o *Multiple Sclerosis Neuropsychological Screening Questionnaire* revele especificidade de 97% (Benedict et al., 2003), a versão de auto-preenchimento não é sensível aos défices cognitivos, sendo influenciada pelo humor e auto-relato da funcionalidade. Apenas a versão para o informador é sensível aos défices neuropsicológicas, mas existe alguma controvérsia na definição de um ponto de corte deste instrumento (O'Brien et al., 2007).

A *performance* no FT não se correlaciona com a duração da doença, o curso da doença, a medicação, a incapacidade, nem com a fadiga. Estes achados estão de acordo com observações anteriores sobre outros instrumentos (Jougleux-Vie et al., 2014; Rao et al., 1991a). De facto, a maioria dos estudos são contraditórios acerca da relação entre incapacidade física e comprometimento cognitivo. Enquanto, Rao et al (1991b) confirmam a inexistência de uma relação, o mesmo autor (Rao et al., 1991a) encontrou uma correlação fraca entre funcionamento neurocognitivo e duração da doença. Além disso, a nossa amostra foi composta por pacientes com EM com baixo nível de incapacidade, o que pode ter influenciado o estabelecimento desta relação.

Talvez devido à inclusão de um leque mais abrangente de funções cognitivas, o desempenho no MoCa, mas não no FT, correlacionou-se com a funcionalidade nas atividades básicas da vida diária. Nenhum dos testes de rastreio revelou correlação com a fadiga. Esta observação reforça os achados de estudos anteriores que apontavam para diferentes bases neuroanatómicas da fadiga e neurocognição (Bester et al., 2013).

O presente estudo confirma a existência de comprometimento cognitivo como uma manifestação clínica da EM (Nocentini et al., 2006) e a importância de se estabelecerem rotinas de *screening* cognitivo para a detecção e intervenção cognitiva precoce.

Em comparação com vários testes de *screening*, o FT tem a vantagem de avaliar uma ampla gama de funções cognitivas num curto período de tempo e de não incluir tarefas de papel e lápis. No entanto, a especificidade do FT pode ser limitada pela não inclusão de um subteste que avalie diretamente a velocidade de processamento de informação, um dos três domínios cognitivos mais comumente afetados (Fisher, 2001).

## 5. Conclusão

O FT é um teste válido, específico, sensível e breve, não dependente das funções sensorio-motoras. Obviamente que o FT não pode substituir uma bateria de avaliação neuropsicológica, mas auxilia na decisão acerca da importância de proceder a uma avaliação mais compreensiva das alterações cognitivas; e pode constituir um indicador fundamental nos casos em que não é necessária muita informação e os recursos económicos e de tempo são escassos.

Em comparação direta com o MoCa, o FT possui vantagens significativas: é mais específico e sensível para a EM; é mais fácil e mais rápido para administrar e pontuar; não requer tarefas de papel e lápis; é adequado para pacientes analfabetos.

Este estudo apresenta como limitação o facto de não avaliar os sintomas depressivos, dado o seu impacto na performance cognitiva (Patti, 2009; Simioni et al., 2007).

Outra limitação é o reduzido número de pacientes com EM Secundária Progressiva e Primária Progressiva, embora Potagas et al. (2008) apontem para um padrão global de défices cognitivos na EM, independentes do curso da doença.

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**Tabela 1 - Caraterísticas dos grupos**

| | Grupo de Controlo (n=19) | Grupo EM (n=30) |
|---|---|---|
| | **M (SD)** | **M (SD)** |
| Idade (anos) | 37,68 (12,09) | 40,47 (11,1) |
| Anos de escolaridade | 11,42 (5,35) | 10,8 (5,5) |

**Tabela 2 - Caraterísticas Clínicas do grupo EM**

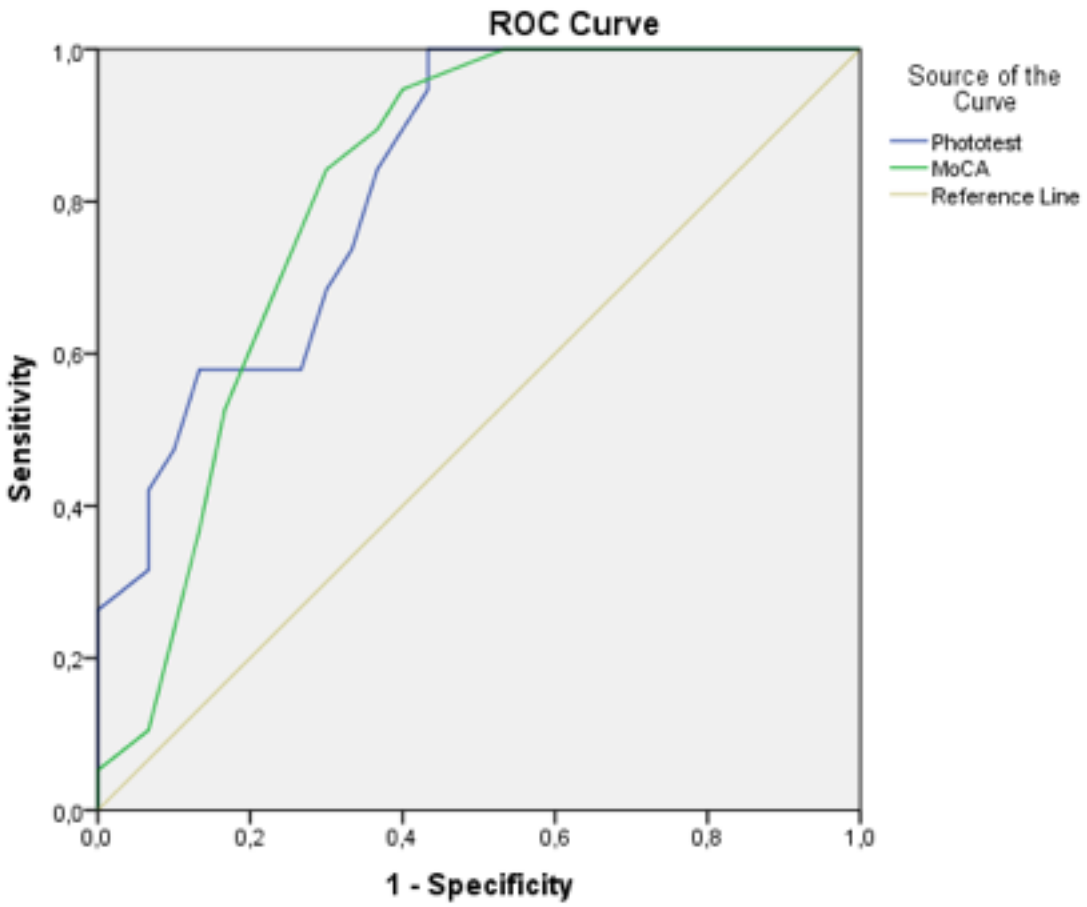
| Variável | EM<br>N = 30 |
|---|---|
| **Padrões de progressão (n, %)** | |
| SP | 5/30, 10.2% |
| RR | 24/30, 49.0% |
| PP | 1/30, 2.0% |
| **Medicação (n, %)** | |
| Medicação da dor | 7/30, 23% |
| Ansiolíticos | 6/30, 20% |
| Antidepressivos | 6/30, 20% |
| Outros | 5/30, 16.7% |
| **Número de surtos** | 8.24 (11.28) [0-60] |
| **Anos de EM** | 11.17 (8.2) [1.5-36] |
| **IB** | 93.67 (11.96) |
| **FSS** | 44.4 (11.77) |
| **EDSS** | 3.97 (2.57) |

*Nota:* Os dados são apresentados como média (SD) e [min-max] salvo indicação em contrário; BI=Barthel Index; SP=Secundária Progressiva; RR=Recidivante-Remitente; PP=Primária Progressiva

**Tabela 3 - Comparações dos resultados obtidos pelos dois grupos nos testes neuropsicológicos**

| | Grupo de controlo (n=19) | Grupo EM (n=30) | | |
|---|---|---|---|---|
| | M (SD) | M (SD) | U | p |
| **Fototest** | | | | |
| Nomeação | 5,26 (0,45) | 5,37 (0,56) | 317 | .434 |
| Recordação livre | 11,05 (01,39) | 9 (2,02) | 118,5 | ≤.001 |
| Recordação Facilitada | 0,47 (0,69) | 1,30 (0,92) | 429 | .002 |
| Fluência Homens | 14,79 (3,31) | 10,63 (3,23) | 109 | ≤.001 |
| Fluência Mulheres | 14,79 (3,17) | 11,27 (3,39) | 126,5 | .001 |
| Total | 46,47 (5,74) | 37,57 (7,01) | 99 | ≤.001 |
| **MoCA** | | | | |
| TMT B | 0,95 (0,23) | 0,53 (0,51) | 167 | .002 |
| Cubo | 0,84 (0,38) | 0,37 (0,49) | 149,5 | .001 |
| Relógio | 2,89 (0,46) | 2,03 (0,77) | 107 | ≤.001 |
| Nomeação | 2,84 (0,38) | 2,6 (0,62) | 232 | .158 |
| Dígitos | 1,84 (0,38) | 1,6 (0,56) | 224 | .111 |
| Cancelamento | 0,89 (0,32) | 0,90 (0,31) | 286,5 | .953 |
| Subtração | 2,89 (0,32) | 2,27 (0,91) | 175 | .006 |
| Frases | 1,53 (0,61) | 1,6 (0,62) | 307 | .594 |
| Fluência Verbal | 0,63 (,49) | 0,27 (0,45) | 181 | .012 |
| Similaridades | 1,42 (0,69) | 1,2 (0,71) | 236 | .273 |
| Recordação diferida | 3,05 (1,13) | 2,17 (1,56) | 196 | .061 |
| Orientação | 5,95 (0,23) | 5,77 (0,63) | 252 | .234 |
| Total | 25,74 (1,69) | 21,27 (4,28) | 107 | ≤.001 |

**Figura 1 - *Receiver operating curve* gerada pelos dois testes neurocognitivos**



**Lista de anexos**

# ANEXO A

Elsevier Editorial System(tm) for Multiple Sclerosis and Related Disorders
Manuscript Draft

Manuscript Number:

Title: Phototest for neurocognitive screening in multiple sclerosis

Article Type: Original Article

Keywords: Multiple Sclerosis; Phototest; Montreal Cognitive Assessment; Expanded Disability Status Scale; Fatigue Severity Scale

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Abstract: Background: Multiple Sclerosis (MS) is one of the most common neurological disorders. Cognitive dysfunction is considered a clinical marker of MS, approximately half of patients with MS have cognitive impairment.´

Objective: The Phototest (PT) is a brief cognitive test, with great diagnostic sensitive, accuracy and cost-effectiveness in detection of cognitive deterioration. Our aim is to test the utility of PT as a neurocognitive screening instrument for MS.

Methods: The study enrolled 30 patients with different types of MS from an outpatient clinic and 19 healthy participants. In complement to PT, the Montreal Cognitive Assessment (MoCA), Barthel Index (BI), Expanded Disability Status Scale (EDSS), Fatigue Severity Scale (FSS), were administered.

Results: The MS group obtained significantly lower results in all domains of PT, except on the naming task. The PT revealed good concurrent validity with MoCA. In direct comparison to MoCA, PT revealed a higher area under the curve and higher levels of sensitivity and specificity for MS neurocognive impairments. A cut-off score of 31 on Phototest showed a sensitivity of 100% and a specificity of 76.7%.

Conclusion: PT is a valid, specific, sensitive and brief test, not dependent on sensoriomotor func-tions. It could be an option for neurocognitive screening in MS, especially in identifying cases for further neuropsychological assessment and intervention.

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**Cover Letter**

Editor-in-Chief of

Multiple Sclerosis and Related Disorders

I hereby sent the original paper entitled "*Phototest for neurocognitive screening in multiple sclerosis*" in order to be considered for publication in Multiple Sclerosis and Related Disorders.

This is an original work that aimed to test the suitability of Phototest as a neurocognitive screening instrument for Multiple Sclerosis in patients from the *Centro Hospitalar Alto Ave* - Portugal, and determine the discriminant validity, sensitivity and specificity of Phototest, as well as its concurrent validity and relation to clinical variables.

This study has not been published before and is not currently being considered for publication elsewhere.

Kind Regards

Thank You

Joana Pinto

Corresponding Author

## Highlights

- The Phototest reveals good psychometric indicators of sensitivity and specificity in neurocognitive assessment of patients with Multiple Sclerosis.
- The Phototest presents good discriminative validity.
- The Phototest shows good concurrent validity with MoCa.

# Phototest for neurocognitive screening in multiple sclerosis

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**Conflicts of interest**

Cristóbal Carnero-Pardo is the creator of Phototest. The remaining authors do not have any conflicts of interest.

## Abstract

Background: Multiple Sclerosis (MS) is one of the most common neurological disorders. Cognitive dysfunction is considered a clinical marker of MS, approximately half of patients with MS have cognitive impairment.

Objective: The Phototest (PT) is a brief cognitive test, with great diagnostic sensitive, accuracy and cost-effectiveness in detection of cognitive deterioration. Our aim is to test the utility of PT as a neurocognitive screening instrument for MS.

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Conclusion: PT is a valid, specific, sensitive and brief test, not dependent on sensoriomotor functions. It could be an option for neurocognitive screening in MS, especially in identifying cases for further neuropsychological assessment and intervention.



**Keywords:** Multiple Sclerosis, Phototest, Montreal Cognitive Assessment, Expanded Disability Status Scale, Fatigue Severity Scale

## 1. Introduction

Multiple Sclerosis (MS) in one of the most common neurological disorders (World Health Organization [WHO], 2006). MS it is more common in locations far from the equator in both hemispheres and it is more common among women than men, suggesting the interaction between genetic and environmental factors. In occidental countries, MS it is the most common cause of disability in young adults (WHO, 2006). It is more frequently diagnosed in subjects between 20 to 40 years old, when patients are economically active thus representing high direct and indirect costs to the national health system. According to recent data it is estimated that there are nearly 5000 persons with MS in Portugal (Machado et al., 2010).

The typical patterns of progression of the disease are: relapsing/remitting; secondary progressive; primary progressive (WHO, 2006). The combination of symptoms varies, resulting in different presentations of the disease (Freeman et al., 2008). Main symptoms include: fatigue and cognitive dysfunction (WHO, 2008; Ko, 1999). Cognitive dysfunction is considered a clinical marker of MS (Nocentini et al., 2006) and it encompasses all the disease stages and types of clinical progression, resulting in limitations in work and social life, independently of the degree of physical disability (Amato et al., 2006).Cognitive impairment affects up to 65% patients and it can occur from the early stages of the disease and tends to worsen over time (Hulst et al., 2014; Amato et al., 2006; Achiron et al., 2005). However due to costs, time consumption and focus on physical disabilities, these impairments are not routinely evaluated (Messinis et al., 2010).

The general intellectual functioning is preserved in the majority of patients (Drew et al., 2008), despite the significant impairment in fluid intelligence (Thornton & Defreitas, 2009). The processing speed of visual and auditory information and verbal fluency are the cognitive domains earlier affected (Nocentini et al., 2006; Achiron et al., 2005). The decrease in processing speed represents the most prominent and common cognitive sign in MS and it is intimately related to the severity of the disease (Hankomäki et al., 2014; Van Schependom et al., 2014a). The decrease in processing speed also impairs working memory encoding (Demaree et al., 1999; Lengenfelder et

al., 2006). Deficits in semantic and phonologic verbal fluency are also frequent among MS patients (Henry & Beatty, 2006). Verbal fluency seems to be impaired at early stage of relapsing/remitting MS, and this impairment increases with MS duration (Brissart et al., 2013). In fact, verbal fluency and processing speed tasks may be amongst the most sensitive neuropsychological measures to cognitive impairment in MS (Henry & Beatty, 2006).

With the progression of disease memory deficits, particularly in encoding, semantic organization (Drake et al., 2006), recall and delayed recall (Achiron et al., 2005; Zakzanis, 2000), became obvious. In delayed recall tasks patients present confabulation errors, consistent with frontal lobe dysfunction (Drake et al., 2006). Furthermore, MS patients show deficits in working memory (Lengenfelder et al., 2006; Nocentini et al., 2006; Zakzanis, 2000), spatial working memory (Foong et al., 1997), verbal long-term memory and visual long-term memory (Andrade et al., 1999), nonverbal memory (Grant et al., 1984), visuospatial short-term and long-term memory (Piras et al., 2003) and in autobiographic memory (Thornton & Defreitas, 2009).

Executive functioning is impaired in the ability to solve problems (Drew et al., 2008; Beatty & Monson, 1996; Piras et al., 2003), in abstract reasoning (Piras et al., 2003), planning, organization, rule change, inhibition, verbal fluency (Drew et al., 2008; Foong et al., 1997), Stroop tasks, cognitive estimate, spatial span and strategies using (Foong et al., 1997). Deficits in divided attention, sustained attention (McCarthy et al., 2005) and in focalized attention (Thornton & Defreitas, 2009) are also frequent.

Visuoconstructive and visuoperceptive abilities are also afected (Vleugels et al., 2000), particularly in color discrimination and in the perception of the Müller-Lyer illusion, as well as in visuospatial integration and discrimination and in complex tasks of facial recognition (Thornton & Defreitas, 2009).

Language deficits are not common (Thornton and Defreitas, 2009), however some authors point to naming difficulties (Drake et al., 2002) and to deficits in linguistic organization, retrieval mechanisms and semantic manipulation and processing (Barwood and Murdoch, 2013).

Cognitive assessment of MS patients it is the first step for the early detection of neurocognitive impairment and for the implementation of therapeutic measures to prevent further decline and decrease the impact of deficits in patients' daily life. However, this assessment is not performed routinely by the lack of sensitive tests, simple, easy to administer and interpret and with good cost-effectiveness relationship (Patti, 2009).

The Phototest (www.fototest.es) is a brief (<3 minutes) cognitive test, easy to administer and assesses several cognitive domains (language, episodic memory and verbal fluency). It has proven great diagnostic sensitive, accuracy and cost-effectiveness in detection of cognitive deterioration in context of mild cognitive impairment (Sánchez et al., 2007; Carnero-Pardo et al., 2007; Carnero-Pardo et al, 2011a, 2011b). Considering costs based on public prices and hospital accounts, the costs involved with the use of the Phototest are considerably lesser in comparison with other screening tests Carnero-Pardo et al, 2011b.; Vilar et al., 2007). Because reading is not required and there are no pencil and paper tasks, this test is suitable for use with illiterates or individuals with a low level of education (Carnero-Pardo et al, 2011a).

Given the clinical characteristics of MS, we aim to test the suitability of Phototest as a neurocognitive screening instrument on the context of MS. Therefore we will determine the discriminant validity, sensitivity and specificity of Phototest, as well as its concurrent validity and relation to clinical variables.

## 2. Method

### 2.1. Participants

The sample comprises two groups: a clinical group composed by 30 subjects (19 woman and 11 men) with a MS diagnosis and a control group constituted 19 healthy subjects (14 women and 5 men) (table 1). Patients were recruited at the neurology outpatient clinic of the *Centro Hospitalar do Alto Ave*, and the subjects of the control group are blood donors.

Individuals with prior history of neuropsychiatric or systemic pathologies liable to directly interfere on neurocognitive functioning were excluded. The alcohol and drugs abuse, illiteracy and sensorio-perceptive changes uncorrected also constitute exclusion criteria.

To assure that the control group was cognitively, individuals with results equal or lower than one standard deviation on the Montreal Cognitive Assessment were excluded from the sample.

Groups do not differ according to age ($t = -2.013$; $p = .485$), gender ($\chi 2 = .567$; $p = .541$) and schooling ( $t = 1.106$; $p = .504$).

## 2.2. Study Measures

### 2.2.1 Phototest

The Phototest is a brief cognitive test, easy to administer that comprises three parts: a naming task with six color photographs of common objects; a categorical verbal fluency task in which subjects must evoke masculine and feminine names; and free and cued recall of the six objects used in the naming task. This test was developed in Spain and it has proven great diagnostic accuracy and effectiveness in the context of cognitive impairment and dementia, even when compared to more traditional screening tests like the Mini Mental State Examination (Carnero-Pardo & Montoro-Ríos, 2004; Carnero-Pardo et al., 2011a; Sánchez et al., 2007) or the Memory Alteration Test (Carnero-Pardo et al., 2011b). It has been demonstrated that cutoff points 26 and 28 offer satisfactory discriminant validity for dementia and cognitive impairment respectively (Carnero-Pardo et al., 2007) and it also has good test-retest and inter-observer reliability (Carnero-Pardo et al., 2011c). This test has normative dates and some psychometric characteristics for Portuguese population (Dias et al., 2014).

### 2.2.2 Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCa) it is a cognitive screening test that assess several cognitive domains, such as: executive functions through an abbreviated form of the trail mak-

ing test part B (TMT B) ; visuospatial abilities through the copy of a tridimensional cube (Cube) and the clock drawing task (Clock); language it is assessed through the naming task of three animals (Naming), the repeating of two complex phrases (Phrases) and a task of phonetic verbal fluency (Verbal Fluency); attention and concentration, are assessed through direct and indirect digit span (Digits), a cancelation (Canceling) and serial subtraction task (Subtraction); abstract thinking by a similarities task (Similarities); memory through the learning and recall of 5 words (delayed recall); temporal and spatial orientation are also assessed through six questions. This test was used because it has high sensitivity to neurocognitive impairments in MS (Aksoy et al., 2013; Dagenais et al, 2013; Kaur et al, 2013) making it a good instrument to establish the concurrent validity of Phototest. MoCA was also used to guarantee the cognitive normality of the subjects of the control group.

### 2.2.3 Fatigue Severity Scale

The Fatigue Severity Scale (FSS) is a self-report scale that assesses the perception of fatigue of MS patients in physical functioning, exercise, work, family and social life. It presents good psychometric properties and it has great construct validity (Pereira & Duarte, 2010). FSS was used in order to characterize the clinical sample and to correlate it with Phototest.

### 2.2.4 Barthel Index

The Barthel Index (BI) evaluates 10 activities: feeding, grooming, toilet use, bathing, dressing, sphincter control, ambulation, transfers, and stair climbing. This test has shown good psychometric qualities for evaluate the functionality in daily life activities in Portuguese patients (Araújo et al, 2007).

### 2.2.5 Expanded Disability Status Scale (EDSS)

The Expanded Disability Status Scale (EDSS) was used to test Phtototest sensitive to neurological incapacity. EDSS it is the most known and widely used scale in quantifying the degree of disability in MS (Sharrack et al., 1999). EDSS assesses eight functional systems: pyramidal, cerebellar, brainstem, sensorial system, bowel and bladder, visual and cerebral (Kurtzke, 1970, 1983). The obtained results range from 0 (normal) to 10 (death due to MS) (Kurtzke, 1970, 1983). EDSS shows good inter and intra-observer reliability and face validity with other disability scales. (Sharrack et al., 1999). The EDSS was used to determine the degree of neurological incapacity of the clinical group and to correlate it with the results on Phototest.

## 2.3. Procedure

This study was proved by the ethical committee of the *Centro Hospitalar do Alto Ave* and all the participants gave their informed consent. All subjects were assessed with the Phototest and MoCA. The IB, FSS and EDSS were applied only to the clinical group. The neuropsychological assessment was conducted in a closed room and during approximately fourteen minutes.

## 2.4 Statistical Analysis

Statistical analysis was carried out using the program IBM Statistics version 21 for Windows.

We have used central tendency and deviation measures to analyze the sample characteristics and the results obtained. The comparison of test performance between groups was performed using the U test of Mann-Whitney. The sensitivity and specificity of Phototest, were determined by a Receiver Operating Curve (ROC). The concurrent validity between Phototest and MoCA, was calculated by the Spearman correlation coefficient.

A value of $p<.05$ was considered statistical significant.

## 3. Results

### 3.1. Clinical Characteristics

Table 2 shows the clinical characteristics of MS group. The majority of the sample it is composed by patients with relapsing-remitting MS. All patients are currently receiving medication for MS. In general, the sample reveals a moderate level of disability and is functional on daily life activities, despite the perception of moderate levels of fatigue.

### 3.2. Comparison between MS patients and controls

MS patients revealed significant lower performance in both neurocognitive tests and in the majority of the tasks. The naming tasks, of Phototest and MoCA, as well as digits, cancelling, phrases repeating, similarities and orientation tasks of MoCA did not show significant differences between groups (Table 2).

### 3.3. Results of analysis of sensitivity and specificity of FT

The results on Phototest correlate positively with MoCA ($\rho = 0.589$; $p = .000$). The performance on MoCA correlates positively with the results in BI ($\rho = 0.362$; $p = .050$). None of the neurocognitive tests showed any correlation to either FSS or EDSS. The same was observed regarding the number of relapses and duration of the disease.

The Phototest presents an area under the curve of .826 (S.E. = .57; $p = .000$), slightest higher than the area under the curve generated by MoCA (AUC= .81; S.E. = .061; $p = .000$), in distinguishing patients from controls (Figure 1).

According to a cutoff of 31 points, Phototest has a sensitivity of 100% and a specificity of 76.7%. A cutoff of 24 points in MoCA represents a sensitivity of 89.5% and a specificity of 36.7%. These cutoff points represent two standard deviations according to the Portuguese normalization studies of these two tests, based on the mean age and years of schooling of our sample.

## 4. Discussion

Phototest proved to be a sensitive and specific instrument to assess general neurocognitive functioning in MS. Although the naming task did not distinguished the two groups the total score of the test revealed higher values of sensitivity and specificity when compared to MoCA. However, the performance on Phototest does not show a relation to fatigue, incapacity in daily life activities, disability and duration of the disease.

Our results showed a good concurrent validity with MoCA, a more extensive test for neurocognitive screening in MS (Aksoy et al., 2013). Perhaps the existence of two tasks of verbal fluency in Phototest has contributed to this finding. As previously stated, verbal fluency is one of the neurocognitve functions earlier affected in MS (Brissart et al., 2013; Henry & Beatty, 2006). Furthermore, the transition between the two tasks of verbal fluency in Phototest requires verbal inhibitory control, as well as rule change. Thus verbal fluency tasks in Phototest indirectly encompass executive components implicated in MS (Drew et al., 2008; Foong et al., 1997). The implicit executive components in verbal fluency are highly influenced by processing speed (Leavitt et al., 2014), another cognitive domain commonly affected in MS (Hankomäki et al., 2014; Van Schependom et al., 2014a).

Processing speed and executive functioning are the main predictors of the performance in episodic memory (Barthelemy et al., 2014). This observation may account to the find that the MS patients have freely recalled fewer objects and have resorted to cued recall more often than controls. Language alterations are not common in MS (Thornton & Defreitas, 2009), thus justifying the absence of differences between groups on the naming task. Naming difficulties are more common in progressive MS (Beatty et al.,1988, 1989) and our sample was mostly composed by patients with relapsing-remittent MS.

Cognitive screening in MS is conditioned by the fact that only a proportion of patients have cognitive deficits, and they are very diverse (Rao, 1990). The use of Phototest can overcome these

problems in the cognitive screening MS, since it evaluates two of the most commonly affected areas: verbal fluency and episodic memory (Rao, 1990; Fisher, 2001; Sepulcre et al 2011).

Phototest revealed higher levels of sensitivity and specificity than MoCA, maybe due to the inclusion of several tasks that have not shown significant differences between groups.

Phototest presents a higher value of sensitivity than most of the cognitive screening tests recommended by Rogers and Panegyres (2007) to the MS: the Symbol Digits Modalities Test (82% and 91%) (Parmenter et al., 2007; Van Schependom et al., 2014b), the PASAT (74%) (Rosti-Otajärvi, 2008), the Clock Drawing Test (92%) (Mohammad-Taghi & Fakhrossadat, 2014) and the Multiple Sclerosis Neuropsychological Screening Questionnaire (83%) (Benedict et al., 2003).

According to specificity, Phototest has higher levels when compared to several screening tests in MS. Good examples are PASAT, with a specificity of 65% (Rosti-Otajärvi, 2008), and the Symbol Digits Modalities Test, with a specificity of 61% (Van Schependon et al., 2014b) . However, when compared to Clock Drawing Test (specificity of 89%) (Mohammad-Taghi & Fakhrossadat, 2014), Phototest shows lower specificity, probably because the clock drawing task requires additional functions such as visuospatial organization, planning and abstraction capacity, intimately related to frontal lobe (Benedict et al., 2002).

Although Multiple Sclerosis Neuropsychological Screening Questionnaire reveals specificity of 97% (Benedict et al., 2003), the self-administered version is not sensitive to cognitive deficits, and it is highly influenced by mood and self-reported functionality. Only the informant-report is sensitive to neuropsychological deficits, but there is some controversy regarding the definition of a cutoff point of this instrument (O'Brien et al., 2007).

The performance on Phototest it is not correlated to the disease length, the course of disease, medication, disability nor with fatigue. This goes in line with previous observations regarding other instruments (Jougleux-Vie et al., 2014; Rao et al., 1991a). In fact, most of the studies are contradictory regarding the relationship between physical disability and cognitive impairment. While Rao et al (1991b) confirm the inexistence of a relationship, the same author (Rao et al. 1991a) found a

weak correlation between neurocognitive functioning and the duration of the disease. Moreover, our sample comprised MS patients with low disability status which may have influenced the establishment of this relation.

Perhaps due to the inclusion of a broader range of cognitive functions, the performance on MoCA but not on Phototest was correlated to the functionality of basic daily life activities. None of the screening tests revealed correlation with fatigue. This observation reinforces previous studies that pointed to different neuroanatomical basis of fatigue and neurocognition (Bester et al., 2013)

This study confirms the existence of cognitive impairment as a clinical manifestation of MS (Nocentini et al., 2006) and the importance in establishing routines of cognitive screening for early detection and cognitive intervention.

Compared to several screening tests, the Phototest has the advantage of assessing a broader range of cognitive functions in a shorter period of time and does not include paper and pencil tasks. However, the specificity of Phototest may be limited by the non-inclusion of a subtest that directly assess the speed of information processing, one of the three cognitive domains most commonly affected (Fisher, 2001).

## 5. Conclusion

The Phototest is a valid, specific, sensitive and brief test, not dependent on sensoriomotor functions. Obviously the Fototest cannot replace a neuropsychological assessment battery, but assists in deciding the importance of conducting a more comprehensive assessment of cognitive changes; and may be a key indicator in cases where is not required much information and economic resources and time are scarce.

In direct comparison to MoCA, Phototest holds significant advantages: It is more specific and sensitive to MS; it is easier and faster to administer and score; does not require pencil and paper tasks; it is suitable for illiterate patients.

This study presents as limitation the fact of it does not assess depressive symptoms, given its impact on cognitive performance (Patti, 2009; Simioni et al., 2007).

Another limitation is the small number of patients with Secondary Progressive and Primary Progressive MS, although Potagas et al. (2008) points a global pattern of cognitive deficits in MS, independent of the course of disease.

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**Table 1 - Characteristics of the groups**

| | Control Group (n=19) | MS Group (n=30) |
|---|---|---|
| | **M (SD)** | **M (SD)** |
| Age (years) | 37,68 (12,09) | 40,47 (11,1) |
| Years of school | 11,42 (5,35) | 10,8 (5,5) |

**Table 2 - Clinical Characteristics of the MS group**

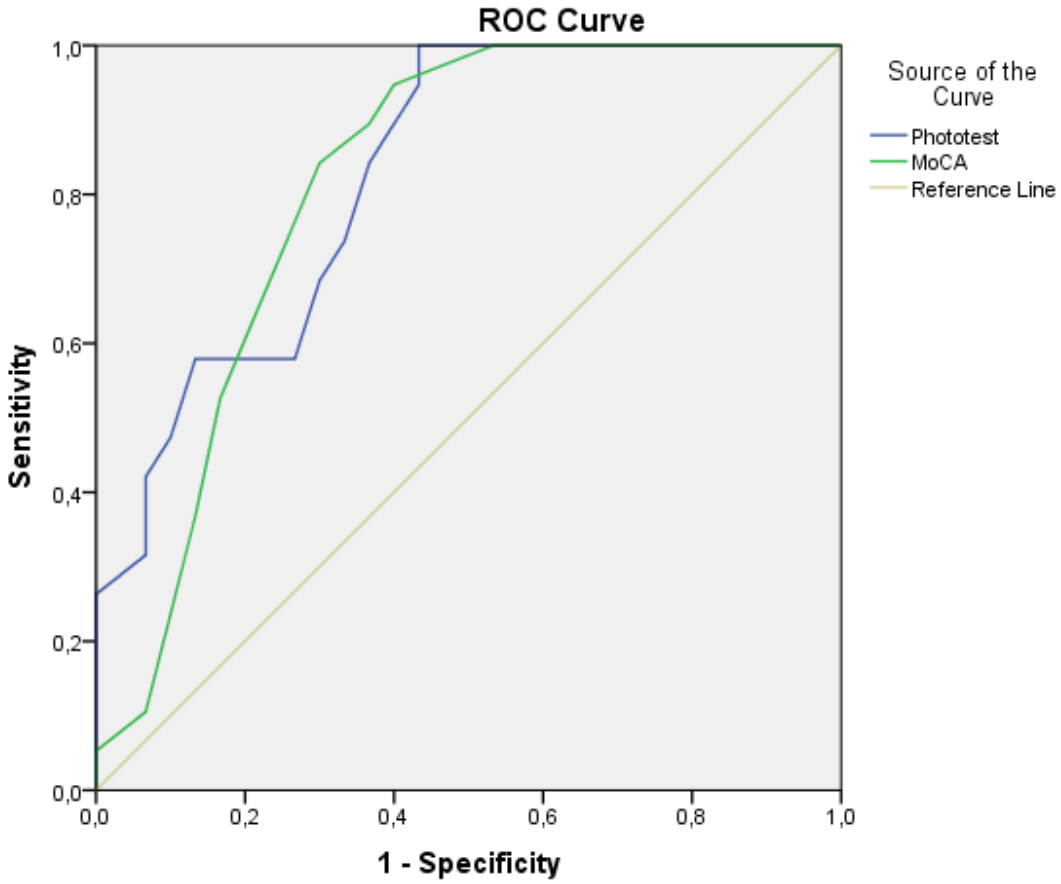
| | **MS**<br>**N = 30** |
|---|---|
| **Patterns of progression (n/ %)** | |
| SP | 5/10.2% |
| RRMS | 24/49.0% |
| PP | 1/2.0% |
| **Medication (n/ %)** | |
| Pain Medication | 7/ 23% |
| Anxiolytics | 6/ 20% |
| Antidepressants | 6/ 20% |
| Others | 5/ 16.7% |
| **Numbers of relapses (M (SD))** | 8.24 (11.28) [0-60] |
| **Years of MS (M (SD))** | 11.17 (8.2) [1.5-36] |
| **BI** | 93.67 (11.96) |
| **FSS** | 44.4 (11.77) |
| **EDSS** | 3.97 (2.57) |

BI=Barthel Index; FSS= Fatigue Severity Scale; EDSS= Expanded Disability Status Scale

**Table 2- Comparisons of the results obtained by the two groups on the neuropsychological tests.**

| | Control Group (n=19) | MS Group (n=30) | | |
|---|---|---|---|---|
| | M (SD) | M (SD) | U | p |
| **Phototest** | | | | |
| Naming | 5,26 (0,45) | 5,37 (0,56) | 317 | .434 |
| Free Recall | 11,05 (01,39) | 9 (2,02) | 118,5 | ≤.001 |
| Cued Recall | 0,47 (0,69) | 1,30 (0,92) | 429 | .002 |
| Fluency Men | 14,79 (3,31) | 10,63 (3,23) | 109 | ≤.001 |
| Fluency Women | 14,79 (3,17) | 11,27 (3,39) | 126,5 | .001 |
| Total | 46,47 (5,74) | 37,57 (7,01) | 99 | ≤.001 |
| **MoCA** | | | | |
| TMT B | 0,95 (0,23) | 0,53 (0,51) | 167 | .002 |
| Cube | 0,84 (0,38) | 0,37 (0,49) | 149,5 | .001 |
| Clock | 2,89 (0,46) | 2,03 (0,77) | 107 | ≤.001 |
| Naming | 2,84 (0,38) | 2,6 (0,62) | 232 | .158 |
| Digits | 1,84 (0,38) | 1,6 (0,56) | 224 | .111 |
| Canceling | 0,89 (0,32) | 0,90 (0,31) | 286,5 | .953 |
| Subtraction | 2,89 (0,32) | 2,27 (0,91) | 175 | .006 |
| Phrases | 1,53 (0,61) | 1,6 (0,62) | 307 | .594 |
| Verbal Fluency | 0,63 (,49) | 0,27 (0,45) | 181 | .012 |
| Similarities | 1,42 (0,69) | 1,2 (0,71) | 236 | .273 |
| Delay recall | 3,05 (1,13) | 2,17 (1,56) | 196 | .061 |
| Orientation | 5,95 (0,23) | 5,77 (0,63) | 252 | .234 |
| Total | 25,74 (1,69) | 21,27 (4,28) | 107 | ≤.001 |

**Figure 1 - Receiver operating curve generated by the two neurocognitive tests**



## Conflicts of interest

Cristóbal Carnero-Pardo is the creator of Phototest. The remaining authors do not have any conflicts of interest.

## ANEXO B

# MULTIPLE SCLEROSIS AND RELATED DISORDERS

AUTHOR INFORMATION PACK

## TABLE OF CONTENTS

**ISSN:** 2211-0348



## DESCRIPTION

**Multiple Sclerosis** is an area of ever expanding research and escalating publications. *Multiple Sclerosis and Related Disorders* is a wide ranging international journal supported by key researchers from all neuroscience domains that focus on MS and associated disease of the **central nervous system**. The primary aim of this new journal is the rapid publication of high quality original research in the field. Important secondary aims will be timely updates and editorials on important scientific and clinical care advances, controversies in the field, and invited opinion articles from current thought leaders on topical issues. One section of the journal will focus on teaching, written to enhance the practice of community and academic neurologists involved in the care of MS patients. Summaries of key articles written for a lay audience will be provided as an on-line resource.

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*Checklist for reporting and reviewing studies of experimental animal models of multiple sclerosis and related disorders*

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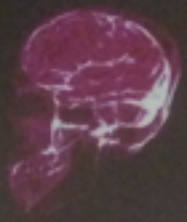
## ANEXO C



# 1.º SIMPÓSIO EUROPEU DE NEUROPSICOLOGIA DO IPNP «O CÉREBRO DO SÉC. XXI»

## CERTIFICADO

Certifica-se que o poster O Rotatest no Rastreio Neurocognitivo na Esclerose Múltipla foi apresentado pelos/as autores/as Joana Pinho, Emanuela Lopes, Ângela Silva, Capucho-Prado, Bruno Polonio, Gaby Gonçalves no

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Porto, 15 de novembro de 2014

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## ANEXO D

# Phototest for neurocognitive screening in multiple sclerosis

Background: Multiple Sclerosis (MS) is one of the most common neurological disorders. Cognitive disfunction is considered a clinical marker of MS, approximately half of patients with MS have cognitive impairment.

Objective: The Phototest (FT) is a brief cognitive test, with great diagnostic sensitive, accuracy and cost-effectiveness in detection of cognitive deterioration. We aim testing the validity of FT in neurocognitive assessment of MS patients, directly comparing with Montreal Cognitive Assessment (MoCa).

Methods: The study involved 30 patients with different types of MS of external neurology consultation of Centro Hospitalar of Alto Ave and healthy participants. In conjunction with the FT and MoCa, were applied Barthel Index (BI), Expanded Disability Status Scale (EDSS), Fatigue Severity Scale (FSS).

Results: The experimental group obtained results significantly lower to control group in all domains of FT, except in Naming subtest. The FT reveals a good concurrent validity with MoCa. We obtained an area under the curve higher than MoCa, with higher significance level for the cutoff points established 31 for FT and 24 for MoCa. To this cutoff points correspond values of sensitivity 100% and of specificity 76,7% in FT, higher than presented in Moca (89,5% e36,7% respectively).

Conclusion: FT is a valid and sensitive test in neurocognitive assessment of MS patients, FT presents as a useful test in neurocognitive assessment of MS patients, once assesses two of the most common affected cognitive domains, verbal fluency and episodic memory.

**Keywords:** Multiple Sclerosis, Fototest, Montreal Cognitive Assessment, Expanded Disability Status Scale, Fatigue Severity Scale