Comparative analysis and predictors of biopsychosocial functioning in various health conditions:

multiple sclerosis and organ transplantation

Tesis realizada bajo la dirección de la Dra. Mª Ángeles Pérez San Gregorio en el Departamento de Personalidad, Evaluación y Tratamiento Psicológicos de la Universidad de Sevilla, que para la obtención del Grado de Doctor y la Mención Internacional en el Título de Doctor presenta D. Eduardo Fernández Jiménez.

En Sevilla, a 23 de abril de 2014.

Desconocemos si la actividad científica, al menos aquella filtrada por los cauces académicos, es la forma más loable del proceder cognoscitivo. Por ende, como mínimo nos esforzaremos porque ésta resulte útil a la sociedad.

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ÍNDICE

1. MARCO LEGISLATIVO DE LA TESIS DOCTORAL

La actual Tesis Doctoral será presentada bajo la modalidad de *tesis por compendio de publicaciones* según el artículo 9 de la normativa reguladora del régimen de Tesis Doctoral (Acuerdo 9.1/CG 19-4-12) de la Universidad de Sevilla. Dichos artículos proceden de dos líneas de investigación centradas en el estudio del funcionamiento biopsicosocial de pacientes con esclerosis múltiple y de personas que han recibido un trasplante de órganos. Esta primera línea de trabajo ha sido posible gracias a la beca-contrato que fue concedida al doctorando dentro del Programa de Formación del Profesorado Universitario (FPU) para el período 2010-2014, financiado por el Ministerio de Educación en la convocatoria del Programa Nacional de Formación de Recursos Humanos de Investigación, del Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica 2008-2011 (Orden EDU/2622/2010, del 1 de octubre de 2010, BOE 11-10-2010). La segunda línea de investigación se enmarca en los dos siguientes proyectos I+D+i financiados que se titulan: a) *"Factores médicos asociados a las fases pre, peri y postoperatoria del implante que influyen en la salud mental y en la calidad de vida de los trasplantados hepáticos"* (2010-2012) (Expediente nº PSI2009-07713), financiado por el Ministerio de Ciencia e Innovación (Resolución de 26 de diciembre de 2008) en la convocatoria de "Ayudas para la realización de proyectos de investigación dentro del Programa Nacional de Proyectos de Investigación Fundamental, en el marco del VI Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica 2008-2011" (BOE 31-12-2008); y b) "*Estrategias para optimizar los resultados en donación y trasplante"* (2003-2005) (Expediente nº C03/03), financiado por el Ministerio de Sanidad y Consumo (Orden SCO/709/2002) en la convocatoria de "Ayudas para el Desarrollo de Redes Temáticas de Investigación Cooperativa" (BOE 3-4-2002). Por consiguiente, se desprende que la presente Tesis Doctoral aúna e integra dos líneas de investigación que tienen un carácter eminentemente multidisciplinar y multicéntrico, de manera que ha sido desarrollada en el seno de diversas unidades de gestión clínica de diferentes instituciones hospitalarias, así como con la colaboración de distintos centros universitarios extranjeros.

2. INTRODUCCIÓN

La calidad de vida relacionada con la salud es un constructo nuclear en el estudio de las condiciones médicas crónicas en general (Sprangers et al., 2000; Varni, Limbers, & Burwinkle, 2007), así como de las dos poblaciones clínicas protagonistas en la presente Tesis Doctoral: la esclerosis múltiple y el trasplante de órganos sólidos.

La esclerosis múltiple es una enfermedad crónica inflamatoria y desmielinizante del sistema nervioso central, de etiología desconocida, que cursa con un amplio repertorio de síntomas y signos propios, así como con condiciones comórbidas, que van desde lo motor, sensorial, urogenital y esfinteriano, hasta lo cognitivo y afectivo (Tullman, 2013). Se trata de la segunda condición neurológica más prevalente entre adultos jóvenes y tiene su inicio entre los 20 y 40 años de edad. A su vez, distintas formas o cursos de enfermedad pueden observarse bajo tal diagnóstico, siendo una enfermedad que presenta gran variedad en términos de severidad entre sus afectados (Tullman, 2013). En concreto, la enfermedad puede iniciarse con períodos alternos de recaídas y remisiones, en las cuales el nivel de discapacidad no aumenta (forma remitente-recidivante); o con un curso progresivo desde el comienzo (forma primaria progresiva), donde raramente se suceden recaídas (de lo contrario, se designaría como forma progresiva recidivante). No obstante, dicho inicio intermitente suele evolucionar, especialmente cuando los pacientes no han recibido ningún tratamiento, hacia una forma progresiva en el 40% de los casos pasados 20 años, en la cual los niveles de deterioro funcional van incrementándose y las recaídas pueden o no intercalarse (forma secundaria progresiva). Por último, la esclerosis múltiple es una enfermedad que afecta más frecuentemente a mujeres que a hombres, con ratios de 3:1 y 3:2 en las formas remitente-recidivante y secundaria progresiva, respectivamente, no existiendo tal asimetría en la forma primaria progresiva. A su vez, una mayor tasa de exacerbaciones se ha observado entre las mujeres (Kalincik et al., 2013).

Con respecto al trasplante de órganos, en la presente Tesis Doctoral nos centraremos en los casos donde el implante fue hepático o renal procedente de donante-cadáver. Se trata de una condición médica donde el paciente ha recibido un injerto, como tratamiento de elección más óptimo hasta la fecha, para abordar su insuficiencia hepática o renal terminal, respectivamente, cuando ya hubieron resultado inviables otras

alternativas terapéuticas. Dada la mayor demanda de órganos que disponibilidad de los mismos, los pacientes han de superar una serie de criterios médicos y psicológicos a lo largo de dos fases: antes de ser incluidos en la lista de espera previa a la intervención del implante, así como una vez admitidos en dicha lista; ambas fases siendo caracterizadas por diferentes niveles de afectación biopsicosocial entre sus afectados (Martín-Rodríguez, Pérez-San-Gregorio, Domínguez-Cabello, Fernández-Jiménez, & Bernardos-Rodríguez, 2014). La relevancia del estudio de la población trasplantada en nuestro país viene apoyada por las siguientes cifras. En España se llevaron a cabo 1093 intervenciones de trasplante hepático y 2552 de trasplante renal en el año 2013 (Organización Nacional de Trasplantes, 2014), siendo el tercer país europeo en intervenciones de trasplante hepático (23.2 por millón en 2012, considerando la procedencia tanto de un donante vivo como cadáver), después de Bélgica (26.1 por millón en 2012) y Croacia (29.1 por millón); así como el tercer país europeo en intervenciones de trasplante renal (54.5 por millón en 2012, considerando la procedencia tanto de un donante vivo como cadáver), después de Países Bajos (57.5 por millón en 2012) y Noruega (59.8 por millón en 2012) (European Committee on Organ Transplantation, 2013).

En ambas poblaciones médicas (esclerosis múltiple y trasplante de órganos) una elevada esperanza de vida está generalmente garantizada; bien porque la experimentada por la mayoría de pacientes con esclerosis múltiple es equivalente a la esperanza de vida de la población general; o bien, en el caso del trasplante de órganos, porque los avances médicos han prolongado exitosamente la supervivencia de más del 50% de los receptores del implante en más de veinte años (Duffy et al., 2010), si bien la esperanza de vida entre trasplantados es inferior a los niveles normativos (van Sandwijk, Bemelman, & Ten Berge, 2013). No obstante, aunque estos logros se explican, entre otros factores, por las estrategias terapéuticas que se han ido implementando (p.e., la inmunoterapia) para ir abordando las complicaciones médicas que estos pacientes han ido padeciendo; tales tratamientos no están exentos de efectos secundarios y eventos indeseados que perturban el funcionamiento cotidiano de los afectados (Kizilisik et al., 2003; Rommer et al., 2014), siendo esta esfera funcional la que precisamente preocupa más a los pacientes, por encima de otros indicadores médicos. Así pues, considerando todo lo anterior, es por lo que la investigación científica ha desplazado el foco de

estudio de la mera maximización de los años de vida y mejora de parámetros fisiológicos (extensión de lesiones cerebrales, número de recaídas, tiempo de supervivencia del injerto, etc.) a la potenciación de la calidad de dicha supervivencia en términos más omnicomprensivos, siguiendo una perspectiva biopsicosocial (Burra & Germani, 2013; Mitchell, Benito-Leon, Gonzalez, & Rivera-Navarro, 2005).

En la dirección de abordar el impacto biopsicosocial que tiene una determinada condición médica en la vida de los pacientes, la investigación empírica se ha desarrollado dentro de los dos siguientes marcos de trabajo: a) comparar diversos grupos de pacientes para determinar el impacto relativo de cada condición médica en la calidad de vida de los mismos; e b) identificar aquellos factores que predicen distintos dominios de la calidad de vida de estos pacientes.

Con respecto a la primera línea de trabajo, en la literatura científica se observa un creciente interés en comparar diferentes poblaciones médicas a fin de determinar si el perfil biopsicosocial identificado es característico de una particular condición clínica (afectación primaria) o si es consecuencia de la circunstancia de estar padeciendo una condición médica crónica en sí misma (afectación secundaria). Así pues, la comparación exclusiva con la población general ha sido cuestionada (Aadahl, Hansen, Kirkegaard, & Groenvold, 2002; Groenvold et al., 1999), ya que ésta no experimenta frecuentemente los estresores crónicos propios de una condición médica discapacitante, los cuales inducen cambios en las expectativas, exigencias vitales y valores de los afectados. Este fenómeno, acuñado como *cambio de respuesta*, promueve una redefinición en el marco de referencia de las personas que han vivido situaciones vitales crónicas y amenazantes (Oort, Visser, & Sprangers, 2009). Estos cambios pueden observarse, por ejemplo, cuando un paciente asume que una plena recuperación ya no es posible; o cuando se ha originado la vivencia de crecimiento personal tras tales situaciones amenazantes, hasta el punto de que los pacientes acaban percibiendo similares o mejores niveles de satisfacción vital que la población general, a pesar de las diversas complicaciones médicas concurrentes, como se ha evidenciado en el caso de trasplantados hepáticos (Kizilisik et al., 2003). En esta misma línea, hallazgos afines han sido asociados con la donación renal en vida. A pesar de las limitaciones físicas o laborales sobrevenidas en los meses posteriores a la intervención quirúrgica (Glotzer,

Singh, Gallichio, Conti, & Siparsky, 2013; Kroencke, Fischer, Nashan, Herich, & Schulz, 2012), ésta es una experiencia que es vivida de forma muy positiva por los propios donantes, aportándole beneficios muy diversos, tales como sentimientos de orgullo; respeto y admiración por parte de los familiares y amigos; mayor valoración de la vida; y un sentimiento de mayor cercanía hacia el receptor (Rodrigue, Schutzer, Paek, & Morrissey, 2011). De ahí que los donantes gocen de similares o mayores niveles de salud mental y calidad de vida que la población sana, ya sea en la fase pre o post-donación (Kroencke et al., 2012; Maglakelidze, Pantsulaia, Managadze, & Chkhotua, 2011).

Como corolario, diversos equipos de investigación han abordado este análisis comparativo entre diversas poblaciones clínicas (Drulovic et al., 2007; Ingerski et al., 2010; Limbers et al., 2011; Sprangers et al., 2000; Varni et al., 2007), incluyendo en las comparaciones a grupos de trasplantados renales (Ingerski et al., 2010; Varni et al., 2007), trasplantados hepáticos (Limbers et al., 2011), así como a pacientes con esclerosis múltiple (Drulovic et al., 2007; Sprangers et al., 2000). En la misma línea, en el seno de nuestro grupo de investigación hemos comparado la calidad de vida y salud mental en mujeres que se habían sometido a tres tipos de cirugías que implicaban diversos grados de manipulación corporal, tales como el implante (trasplante de un órgano), la extracción (mastectomía debida a cáncer de mama) y reconstrucción (reconstrucción mamaria debida a cáncer de mama) (Pérez-San-Gregorio, Fernández-Jiménez, Martín-Rodríguez, Borda-Mas, & Rincón-Fernández, 2013); así como se comparó la calidad de vida y salud mental entre trasplantados y pacientes con patología pulmonar (Galán-Rodríguez, Pérez-San-Gregorio, Martín-Rodríguez, & Borda-Mas, 2008). Tanto en nuestros trabajos como en aquellos realizados por otros equipos de investigación, los trasplantados mostraron mejores niveles de calidad de vida y salud mental que otras condiciones médicas en algunas dimensiones (mastectomía tras cáncer de mama, enfermedad pulmonar obstructiva crónica descompensada); pero también niveles inferiores que otras poblaciones clínicas en otros dominios de calidad de vida (reconstrucción mamaria tras cáncer, enfermedad intestinal inflamatoria). Asimismo, pacientes con esclerosis múltiple mostraron peores niveles de calidad de vida en las subescalas del Cuestionario de Salud SF-36 (Alonso, Prieto, & Antó, 1995) Funcionamiento físico y social con respecto a pacientes con diabetes tipo II (Drulovic et

al., 2007), pero ninguna otra diferencia en las restantes dimensiones; así como mostraron peores niveles generales de funcionamiento biopsicosocial que pacientes con hipertensión o problemas endocrinos (Sprangers et al., 2000). Además, cuando los pacientes con esclerosis múltiple fueron comparados con pacientes con otras condiciones neurológicas, los primeros mostraron peores niveles generales de calidad de vida que aquellos afectados por enfermedades neuromusculares (Sprangers et al., 2000).

Siguiendo este mismo marco de trabajo, en la presente Tesis Doctoral se propone el estudio comparativo de la calidad de vida en pacientes con esclerosis múltiple con otras condiciones médicas crónicas, como son las personas que han recibido un trasplante hepático o renal de donante-cadáver.

En la literatura científica no existen trabajos que aborden la comparación del bienestar biopsicosocial entre estas dos condiciones médicas. Por el contrario, los escasos estudios que vincularon la esclerosis múltiple con el trasplante de órganos sólidos han sido enfocados desde una perspectiva meramente médica en los términos siguientes. Por una parte, tanto los trasplantados como los pacientes diagnosticados de esclerosis múltiple se someten, en términos generales, a tratamientos farmacológicos afines, esto es, la inmunoterapia. No obstante, incluso el mismo principio activo farmacológico podría ser aplicado en ambas poblaciones clínicas, como es el caso de Tacrolimus, Micofenolato de mofetilo (Behrbohm et al., 2007; Strader, Pearce, & Oberlies, 2011; Yoshida, Devonshire, & Prout, 2004) o los corticosteroides sintéticos. Por consiguiente, ambas condiciones médicas podrían exponerse a similares efectos secundarios, así como compartir inusuales, si bien fatales, complicaciones médicas, p.e., la leucoencefalopatía multifocal progresiva (Mateen et al., 2011), como pudiera darse la posibilidad cuando los pacientes con esclerosis múltiple son tratados con el anticuerpo monoclonal humanizado Natalizumab. Asimismo, dado que estos tratamientos inmunosupresores/inmunomoduladores han de administrase a largo plazo, ambas poblaciones pueden sufrir recurrentes infecciones y enfermedades oportunistas con el transcurso del tiempo. Además, ambas condiciones médicas pueden padecer eventos que amenacen su integridad física y calidad de vida como pueden ser el rechazo del injerto, en el caso de los trasplantados, o una exacerbación de la enfermedad, con respecto a los pacientes neurológicos. Cabe destacar aquí que tanto un rechazo agudo

del órgano como las recaídas en esclerosis múltiple son complicaciones clínicas experimentadas con cierta frecuencia y ambas suelen ser tratadas con corticosteroides sintéticos, a lo que habría que sumar sus posibles efectos secundarios derivados (Kizilisik et al., 2003; van Sandwijk et al., 2013). Por tanto, ambos grupos clínicos se exponen a estresores significativos que imponen reajustes a lo largo del tiempo e inducen sentimientos de incertidumbre. De ahí que la calidad de vida en ambas poblaciones no siga una trayectoria predecible.

Así pues, se pone de manifiesto que el estudio conjunto de pacientes diagnosticados con esclerosis múltiple y de personas que han recibido un trasplante de órgano es un marco comparativo idóneo para la evaluación del impacto diferencial que ejerce cada una de estas condiciones clínicas en la calidad de vida de los afectados por las mismas. De especial relevancia es este análisis comparativo homogeneizando la terapia farmacológica, dada la variedad de efectos secundarios y complicaciones médicas que pueden derivarse de los tratamientos inmunomoduladores e inmunosupresores y que, por consiguiente, podrían afectar en una magnitud análoga a ambas condiciones clínicas (Kizilisik et al., 2003; Kugler et al., 2009). Asimismo, dado que el trasplante de órganos no es una condición neurológica, se podría discernir, a igualdad de otros factores, si el deterioro afectivo padecido por los pacientes con esclerosis múltiple tiene etiología fundamentalmente neurológica o es reactivo al hecho de estar padeciendo una condición crónica discapacitante, lo cual es un debate científico recurrente (Dalton & Heinrichs, 2005; Holden & Isaac, 2011).

En este contexto, los únicos estudios que han comparado ambas poblaciones clínicas en términos biopsicosociales son los realizados recientemente por nuestro equipo de investigación. En un primer trabajo, se comparó la calidad de vida de los pacientes diagnosticados de esclerosis múltiple con trasplantados hepáticos a través de un diseño transversal con emparejamiento por género (Fernández-Jiménez et al., 2012). En segundo lugar, el análisis comparativo de la calidad de vida implicó a trasplantados renales emparejados por género y homogeneizados en función de la edad y estatus laboral, mediante un diseño longitudinal con una diferencia de seis meses entre medidas (Fernández-Jiménez, Pérez-San-Gregorio, Martín-Rodríguez, Pérez-Bernal, & Izquierdo, 2013). Ambos trabajos enfatizaron la significación clínica de sus resultados

al ser comparados con los niveles de calidad de vida de una muestra representativa de la población general española con edad afín (Alonso et al., 1998).

En torno al segundo marco de trabajo, esto es, el de identificar aquellos factores que predicen distintas dimensiones biopsicosociales en personas aquejadas por una condición médica; desde nuestro equipo de investigación hemos realizado diversas contribuciones con esta finalidad en el ámbito del trasplante de órganos, las cuales van más allá de la mera comparación entre fases pre y post-trasplante (Domínguez-Cabello, Martín-Rodríguez, Pérez-San-Gregorio, Fernández-Jiménez, Bernardos-Rodríguez, et al., 2012; Martín-Rodríguez et al., 2014). En este sentido, hemos identificado cómo la etiología de la enfermedad hepática desencadenante del trasplante (viral versus etílica) se asocia a una peor calidad de vida y salud mental en el caso del Virus de la Hepatitis C, independientemente de si los pacientes fueron trasplantados o no (Pérez-San-Gregorio, Martín-Rodríguez, Domínguez-Cabello, Fernández-Jiménez, Borda-Más, et al., 2012). A su vez, hemos probado cómo la sintomatología ansioso-depresiva y el dolor se vinculan a niveles más desfavorables en otras dimensiones de calidad de vida, tanto en diseños transversales como longitudinales (Martín-Rodríguez, Fernández-Jiménez, Pérez-San-Gregorio, Pérez-Bernal, & Gómez-Bravo, 2013; Pérez-San-Gregorio, Martín-Rodríguez, Domínguez-Cabello, Fernández-Jiménez, & Pérez-Bernal, 2012). Por otra parte, hemos demostrado cómo dentro de la población de trasplantados hay gran variabilidad en términos de calidad de vida y salud mental, de forma que se puede encontrar mayor similitud entre pacientes en fase pre y post-trasplante cuando éstos últimos se perciben con un peor status de salud global (Martín-Rodríguez, Pérez-San-Gregorio, Domínguez-Cabello, Fernández-Jiménez, & Pérez-Bernal, 2012; Pérez-San-Gregorio, Martín-Rodríguez, Domínguez-Cabello, Fernández-Jiménez, & Bernardos-Rodríguez, 2013). Y por último, hemos identificado estilos de afrontamiento adaptativos que son usados en menor medida entre pacientes cirróticos, cuando sus familiares presentan niveles clínicos de ansiedad (Domínguez-Cabello, Martín-Rodríguez, Pérez-San-Gregorio, Fernández-Jiménez, Sousa-Martín, et al., 2012).

En lo que concierne a la presente Tesis Doctoral, nos centramos particularmente en la esclerosis múltiple de cara a identificar predictores del funcionamiento biopsicosocial de estos pacientes, concretamente en el dominio del dolor. En este contexto, las

variables afectivas han sido destacadas como los predictores tratables más relevantes de la calidad de vida de estos pacientes neurológicos (D'Alisa et al., 2006). Específicamente, la sintomatología depresiva se ha postulado como factor clave en la explicación del deterioro biopsicosocial de las personas con esclerosis múltiple, siendo una enfermedad donde aproximadamente el 50% de los pacientes padece depresión a lo largo de su vida, si bien ésta ha estado siendo infradiagnosticada y escasamente tratada en las saturadas unidades de neurología (Feinstein, 2011). Menor atención ha recibido la sintomatología ansiosa en esta condición neurodegenerativa a pesar de su relevancia clínica, puesto que su comorbilidad con la depresión aumenta la frecuencia de ideación suicida en estos pacientes (Sá, 2008).

Uno de los conceptos estrechamente vinculados a las variables afectivas en la literatura científica ha sido el de alexitimia. Este constructo abarca dificultades en la identificación de sentimientos; en diferenciarlos de las sensaciones somáticas vinculadas con la activación emocional; dificultades en verbalizar dichos sentimientos a otras personas; restricción en la capacidad para la ensoñación y fantasía; así como un estilo de pensamiento externamente orientado (Bagby, Parker, & Taylor, 1994). Si la alexitimia es un factor predisponente de trastornos del espectro ansioso y depresivo, si ésta es secundaria y dependiente del estado afectivo, o si ambas explicaciones son igualmente plausibles; los resultados de la literatura científica no son aún concluyentes, así como han sido originados en el seno de los mismos grupos de investigación, por lo que el debate científico sigue abierto. En resumen, con los hallazgos acumulados hasta la fecha, podría apuntarse que la alexitimia es una variable secundaria de los trastornos ansiosos (Marchesi, Fonto, Balista, Cimmino, & Maggini, 2005; Marchesi et al., 2014), con los cuales, a su vez, presenta cierto solapamiento de contenido debido a la dimensión alexitímica que versa sobre las dificultades en la identificación de sentimientos (Marchesi, Brusamonti, & Maggini, 2000). En la misma línea, su rol predisponente en el desarrollo de trastornos depresivos está igualmente cuestionado (Honkalampi et al., 2010; Marchesi, Bertoni, Cantoni, & Maggini, 2008), al igual que su estatus como constructo independiente de este espectro psicopatológico del estado de ánimo (Hintikka, Honkalampi, Lehtonen, & Viinamaki, 2001; Marchesi et al., 2000), hasta el punto de que la contribución hereditaria en el desarrollo de la alexitimia se ve reducida cuando se elimina la covariabilidad que mantiene con la sintomatología

depresiva (Picardi et al., 2011). Estos hallazgos y los derivados de otros estudios fundamentan el papel mediador de la sintomatología depresiva entre la alexitimia y otros resultados de salud, como es el dolor (Saariaho, Saariaho, Mattila, Karukivi, & Joukamaa, 2013). No obstante, varios de estos estudios presentan las siguientes limitaciones. En primer lugar, en el estudio más reciente de esta línea de investigación (Marchesi, Ossola, Tonna, & De Panfilis, in press) se incumplieron supuestos básicos del Análisis de Covarianza (ANCOVA), como es el de independencia entre el factor y la covariables (Miller & Chapman, 2001), teniéndose que asumir con cierta cautela los hallazgos obtenidos. Por otra parte, algunos de estos trabajos han estudiado exclusivamente mujeres embarazadas antes, durante y tras la remisión de sus trastornos afectivos (Marchesi et al., 2008; Marchesi et al., 2014), por lo que se desconoce el papel que podrían haber jugado los cambios hormonales en la relación entre la alexitimia y la psicopatología afectiva, comprometiendo seriamente así la generalización de los resultados. Por último, los estudios analítico-factoriales mencionados siguen diseños transversales, por lo que el supuesto solapamiento de constructos apunta únicamente a una mera correlación concurrente entre variables y no supone esclarecimiento alguno acerca de la precedencia temporal, así como tampoco de la posible relación causal entre la alexitimia y el afecto negativo.

El constructo de la alexitimia ha recibido escasa atención en esclerosis múltiple, si bien esta dimensión ha sido implicada en numerosas condiciones de salud tales como el trasplante hepático (Romo, Page, & Gell, 2011); enfermedades *osteomusculares y del tejido conjuntivo* como la artritis reumatoide, lupus eritematoso sistémico (Vadacca et al., in press) y la fibromialgia (Huber, Suman, Biasi, & Carli, 2009); *neoplásicas* (Porcelli, Tulipani, Maiello, Cilenti, & Todarello, 2007); *neurológicas* como la tortícolis espasmódica idiopática (Scheidt et al., 1999); *digestivas* como el síndrome del colon irritable y las enfermedades intestinales inflamatorias (enfermedad de Crohn y colitis ulcerosa) (Bengtsson, Sjöberg, Candamio, Lerman, & Ohlsson, 2013); anomalías *dentofaciales* como el trastorno temporomandibular (Glaros & Lumley, 2005); *cardiovasculares*, *cerebrovasculares*, *infecciosas* (VIH), *endocrinológicas* (diabetes), *dolor crónico* y, por supuesto, *psicopatológicas* (Lumley, Neely, & Burger, 2007). Por consiguiente, se pone de manifiesto que el estudio de las dificultades en la identificación y verbalización afectiva ha dejado atrás su mera vinculación a los clásicos trastornos

psicosomáticos unidos a mecanismos de defensa activos en la represión y evitación emocional; para evolucionar hacia un amplio paradigma de investigación, el del constructo de la alexitimia, en el que se ponen de relieve déficits en la consciencia y regulación emocional que intervienen o se manifiestan en tan numerosas y variadas disfunciones de salud (Lumley et al., 2007; Zackheim, 2007); y que ha generado multitud de líneas de trabajo en áreas de conocimiento tan diversas como la Psicofisiología, Neurociencias, Psicología Básica, Psicología Cultural, etc.

En los escasos estudios donde la alexitimia se ha investigado en esclerosis múltiple, los resultados han evidenciado una correlación positiva entre este constructo y la sintomatología ansioso-depresiva (Bodini et al., 2008; Gay, Vrignaud, Garitte, & Meunier, 2010), así como un mayor deterioro en el reconocimiento afectivo de caras y mayores niveles de alexitimia por parte de los pacientes con esclerosis múltiple frente a participantes controles sin patología (Prochnow et al., 2011).

Los estudios disponibles hasta la fecha en esclerosis múltiple han empleado la Escala de Alexitimia de Toronto, en su versión de 20 ítems (TAS-20). Ésta es el instrumento más frecuente y ampliamente usado para evaluar este constructo y fue diseñado para abarcar contenidos tales como las dificultades en identificar y describir sentimientos, así como la tendencia a centrarse en eventos externos de naturaleza no afectiva, en detrimento de las vivencias subjetivas y sentimientos; por lo que la capacidad reducida para la imaginación fue excluida en dicha versión de la escala (Bagby et al., 1994). Todos estos estudios, aunque escasos, han sido llevados a cabo sin haber evaluado aún la estructura factorial de la TAS-20 en dicha población neurológica y, además, las anteriores versiones de la escala en español necesitan modificaciones. Así pues, hay que tomar con cautela aquellos estudios que han analizado el valor predictivo de las distintas subescalas de las TAS-20 hasta que no se pruebe su validez factorial en esclerosis múltiple, máxime cuando la estructura factorial de este instrumento varía en función de la muestra clínica (Kooiman, Spinhoven, & Trijsburg, 2002; Müller, Bühner, & Ellgring, 2003; Pérez-Rincón et al., 1997) o de la población general (Hintikka et al., 2001) en la que se analiza. Por consiguiente, esta laguna en la literatura científica no ha de ser cubierta meramente por fines psicométricos, sino igualmente por fines clínicos, esto es, el de determinar qué dimensiones de la TAS-20 son diferencialmente asociadas

a distintos constructos de salud (Briggs & Cheek, 1986); sobre todo, cuando las *dificultades en identificar y describir sentimientos* son dimensiones de naturaleza afectiva y el *pensamiento externamente orientado* constituiría la faceta más cognitiva del constructo. En este sentido, otro de los trabajos desarrollados en el seno de nuestro equipo de investigación, que también forma parte de la presente Tesis Doctoral, se materializó en el primer estudio de la estructura factorial de la TAS-20 en esclerosis múltiple, proponiendo una nueva versión en español, la TAS-20-S (Fernández-Jiménez, Pérez-San-Gregorio, Taylor, et al., 2013), que mejora las versiones previas creadas en nuestro país (Martínez-Sánchez, 1996; Páez et al., 1999).

Siguiendo esta misma dirección de abordar la utilidad clínica de las diferentes subescalas de un instrumento, entre las diversas áreas donde se ha investigado el valor predictivo diferencial de las distintas dimensiones de la TAS-20 y la alexitimia en general, el dolor ha sido una de las más destacadas (Glaros & Lumley, 2005; Hosoi et al., 2010; Lumley, Smith, & Longo, 2002; Makino et al., 2013; Mehling & Krause, 2005; Saariaho et al., 2013; Shibata et al., 2014; White, McDonnell, & Gervino, 2011; Yalug et al., 2010). Esta diversidad de investigaciones contrasta con un único trabajo en esclerosis múltiple que incluyó el constructo de la alexitimia en el estudio del dolor, centrándose fundamentalmente en la migraña (Villani, Prosperini, Pozzilli, Salvetti, & Sette, 2011). Por consiguiente, el análisis del impacto de la alexitimia en el dolor en pacientes con esclerosis múltiple es un campo de estudio completamente inexplorado, a pesar de que dicho síntoma requiera un ingente esfuerzo asistencial y de investigación, al ser bastante frecuente y discapacitante en esta condición neurodegenerativa. En concreto, recientes hallazgos meta-analíticos estiman una frecuencia de dolor, en general, del 62.8% (intervalo de confianza al 95%: 55.1 – 70.3%) en esclerosis múltiple (Foley et al., 2013), así como otros estudios destacan su impacto en la calidad de vida de estos pacientes (Hadjimichael, Kerns, Rizzo, Cutter, & Vollmer, 2007; O'Connor, Schwid, Herrmann, Markman, & Dworkin, 2008; Svendsen, Jensen, Hansen, & Bach, 2005).

Sin embargo, y a pesar de la gran cantidad de trabajos acumulados sobre alexitimia en la literatura científica, recientes estudios de revisión siguen aún reclamando nuevos estudios longitudinales para determinar el rol del constructo alexitímico en el desarrollo

de diversos problemas de salud (Kojima, 2012). En esta línea se enmarca el cuarto trabajo que constituye la presente Tesis Doctoral, donde el objetivo fue predecir la intensidad del dolor y la interferencia del mismo en diferentes esferas de la vida cotidiana de pacientes con esclerosis múltiple cuando hubieron transcurrido seis y dieciocho meses de la línea base del estudio. Para ello se examinó la importancia relativa de las variables sociodemográficas asociadas a estas variables criterio, tales como la edad, género y nivel educativo; así como de aquellas de naturaleza afectiva, como son la sintomatología ansioso-depresiva y los diferentes dominios de la alexitimia medidos por la TAS-20-S.

No obstante, el peso diferencial de cada uno de los predictores no fue abordado siguiendo los métodos estadísticos tradicionalmente aplicados para tal finalidad, sino que nos basamos en métodos más adecuados en la asignación de la importancia de cada predictor en el modelo (Tonidandel & LeBreton, 2011). En concreto, partimos del modelo de pesos relativos de Johnson (Johnson, 2000), el cual aborda con mayor validez ecológica la frecuente circunstancia con respecto a la interacción entre variables predictoras (Tonidandel, Lebreton, & Johnson, 2009). Así pues, en lugar de neutralizar o mantener constante, de forma artificial, el resto de predictores de un modelo, este método de pesos relativos considera tanto ortogonal como conjuntamente cada regresor con respecto a los demás. Por consiguiente, mientras que los tradicionalmente usados coeficientes de regresión estandarizados (beta) simplemente asignan el peso que tiene cada variable en la ecuación de regresión y son desvirtuados ante fenómenos de supresión (Kraha, Turner, Nimon, Zientek, & Henson, 2012); los pesos relativos asignan una contribución al predictor más proporcionada, teniendo en cuenta tanto su única contribución como aquella que posee en concierto con otros regresores. Así pues, los pesos betas son una representación artificial de la contribución que hace cada variable en la varianza estimada de un modelo.

En resumen, en la presente Tesis Doctoral se proponen cuatro investigaciones empíricas, tres de ellas ya publicadas en revistas indexadas en la *Journal Citation Reports* (JCR) de *ISI Web of Knowledge*, en las que: a) se comparó la calidad de vida de pacientes diagnosticados de esclerosis múltiple con trasplantados hepáticos, de forma transversal, y b) con trasplantados renales, de forma longitudinal (transcurridos seis

meses desde la línea base del estudio); c) así como se comparó el valor predictivo de la sintomatología ansioso-depresiva y de las distintas subescalas de la TAS-20, transcurridos seis y dieciocho meses, en la percepción de dolor de pacientes con esclerosis múltiple, d) habiendo probado previamente la estructura factorial de este último cuestionario. En la Tabla 1 se resumen los objetivos (generales y específicos), así como los aspectos que conciernen al método (diseño, tamaño muestral, análisis estadísticos) de cada uno de los cuatro trabajos que conforman esta Tesis Doctoral.

Tabla 1. Objetivos y método de los trabajos que conforman la presente Tesis Doctoral

Objetivo general	Determinar el impacto relativo de la esclerosis múltiple –EM– y el trasplante de órganos (hepático –ToH– y renal –ToR–) en la calidad de vida de los pacientes.	
Título del trabajo	*Comparison of quality of life between two clinical conditions with immunosuppressive therapy: Liver transplantation and multiple sclerosis*	*Evolution of quality of life in renal transplant recipients and patients with multiple sclerosis: A follow-up study*
Objetivos específicos	-Comparar la calidad de vida entre EM y ToH transversalmente. -Determinar la significación clínica de los resultados con respecto a una muestra representativa de la población general española con edad afín.	-Comparar la calidad de vida entre EM y ToR longitudinalmente. -Determinar la significación clínica de los resultados con respecto a una muestra representativa de la población general española con edad afín.
Método	-Diseño transversal. -*n* = 62 pacientes (31 EM y 31 ToH). -Emparejamiento por género. -ANCOVA: tiempo desde diagnóstico EM/intervención trasplante como covariable.	-Diseño longitudinal (línea base –T1– y transcurridos 6 meses –T2–). -*n* = 60 pacientes (30 EM y 30 ToR) en T1 y T2. -Emparejamiento por género. -Homogeneización por edad y status laboral. -ANCOVA mixto: edad como covariable.
Objetivo general	Identificar factores que predicen uno de los dominios de la calidad de vida, esto es, el dolor, en pacientes con esclerosis múltiple –EM–.	
Título del trabajo	*Psychometric properties of a revised Spanish 20-item Toronto Alexithymia Scale adaptation in multiple sclerosis patients*	*A relative importance analysis of alexithymia and negative affect on pain intensity and pain interference in multiple sclerosis: An 18-month follow-up study*
Objetivos específicos	-Mejorar la versión en español de la Escala de Alexitimia de Toronto (TAS-20-S). -Estudiar la validez factorial de la TAS-20-S en una muestra de pacientes con EM.	-Determinar longitudinalmente la importancia relativa de variables sociodemográficas y afectivas en la predicción de la intensidad e interferencia funcional del dolor en EM.
Método	-Diseño transversal. -*n* = 221 pacientes con EM (*n* = 85 retest). -Análisis factorial confirmatorio. -Análisis de fiabilidad (consistencia interna y test-retest).	-Diseño longitudinal (línea base –T1–, transcurridos 6 meses –T2– y 18 meses –T3–). -*n* = T1: 211 pacientes; T2: 200 pacientes; y T3: 201 pacientes con EM. -Análisis de pesos relativos.

3. OBJECTIVES

The present Ph.D. dissertation had a twofold general objective:

1) to determine the relative impact of multiple sclerosis and organ transplantation on patients' quality of life.

2) to identify factors predicting a quality-of-life domain, i.e., pain, in patients with multiple sclerosis.

In particular, these aims were operationalized in the following six specific objectives:

1.1.) to cross-sectionally compare quality of life of patients with multiple sclerosis and cadaveric liver transplant recipients;

1.2.) to longitudinally compare quality of life of patients with multiple sclerosis and cadaveric renal transplant recipients in two assessment points (6 months between both phases);

1.3.) to determine the clinical significance of the levels of quality of life of patients with multiple sclerosis and cadaveric transplant recipients (hepatic and renal) regarding the levels of quality of life of a representative age-adjusted sample of the general Spanish population;

2.1.) to develop an improved Spanish adaptation of the 20-item Toronto Alexithymia Scale named the TAS-20-S;

2.2.) to assess the factorial validity and reliability of the TAS-20-S in a sample of patients with multiple sclerosis;

2.3.) to longitudinally analyze the relative importance of alexithymia and negative affect on pain intensity and pain interference in patients with multiple sclerosis, taking into account relevant sociodemographic variables (age, gender and years of education) and

measurement error following a 18-month follow-up design (baseline, 6 and 18 months later).

4. TRABAJOS QUE CONFORMAN LA TESIS DOCTORAL

4.1. Primer trabajo titulado "*Comparison of quality of life between two clinical conditions with immunosuppressive therapy: Liver transplantation and multiple sclerosis*"

Este trabajo corresponde al artículo publicado que se referencia a continuación:

Fernández-Jiménez, E., Pérez-San-Gregorio, M. A., Martín-Rodríguez, A., Domínguez-Cabello, E., Navarro-Mascarell, G., & Bernardos-Rodríguez, A. (2012). Comparison of quality of life between two clinical conditions with immunosuppressive therapy: Liver transplantation and multiple sclerosis. *Transplantation Proceedings*, *44*, 2609-2611.

Abstract

We aimed to compare quality of life in two clinical conditions treated with immunosuppressants: cadaveric liver transplant recipients and multiple sclerosis patients. We also assessed the clinical significance of these results regarding a representative age-adjusted sample of the general Spanish population. Using a cross-sectional design, the SF-36 Health Survey was used to evaluate 62 patients with these chronic conditions (31 in each group) who were matched for gender. An analysis of covariance was performed to control for the influence of time from multiple sclerosis diagnosis and liver transplantation surgery until assessment. Student *t* test of covariate-adjusted mean values was used as the statistical test and Cohen's *d* effect size index, to assess the magnitude of intergroup differences and assess clinical significance. Significantly worse scores were observed among the neurological patients compared with transplant recipients regarding role-physical (p = .038), general health (p = .003), vitality (p = .034), and physical functioning (p = .049), with medium effect sizes (Cohen's *d*s from –0.511 to –0.785). Against normative values, liver transplant recipients displayed relevant differences in all SF-36 subscales (Cohen's *d*s from –0.569 to –0.974) except for mental health (small effect size). Likewise, multiple sclerosis patients showed much greater differences versus the general population (Cohen's *d*s from –0.846 to –1.760). In conclusion, liver transplant recipients showed better quality of life than multiple sclerosis patients (medium effect sizes) in physical quality-of-life dimensions. Interestingly, despite having controlled for time from diagnosis/transplantation, both medical conditions showed clinically significant impairments (large and medium effect sizes) in physical and psychosocial quality-of-life domains. We concluded that transplant recipients belong to a population that still requires special health care because, even after having undergone their treatment of choice, they do not achieve normal levels of biopsychosocial functioning.

Introduction

The assessment of quality of life (QoL) among liver transplant recipients versus pretransplantation patients or the general population has been widely studied (Pérez-San-Gregorio et al., 2012; Telles-Correia, Barbosa, Mega, Monteiro, & Barroso, 2011). However, the general population does not usually undergo the chronic stressors related to a lethal or disabling disease. Consequently, it is sometimes reported that liver transplant recipients enjoy better QoL than the general population (Kizilisik et al., 2003), maybe due to phenomena such as the response-shift, which is explained by patients' frames of reference having changed after the experience of a chronic disabling disease, ie, accepting that full recovery is impossible. This possibility might be observed when they answer questionnaires (Oort, Visser, & Sprangers, 2009). One solution for a more relevant comparison would be an evaluation with reference to another chronic disease group with some similarities. In this sense, multiple sclerosis (MS) may be a valid contrast group because both they and liver transplant recipients are immunocompromised, which could induce similar therapy-related complications (Mateen et al., 2011). Therefore, we sought to compare QoL between liver transplant recipients and MS patients and assess the clinical significance of these results regarding the general Spanish population of similar age.

Methods

Selection and Description of Participants and Statistical Techniques

The participant sample comprised 31 MS patients (excluding the primary progressive type), whose mean age was 37.58 years (*SD* = 8.51; range, 20 to 54 years), and 31 cadaveric liver transplant recipients (excluding hepato-renal and retransplantation cases), whose mean age was 45.35 years (*SD* = 11.11; range, 22 to 59 years). The groups were matched for gender (22 women and 9 men). The general inclusion criteria were: a cognitive level allowing completion of the questionnaire and not having suffered a recent loss of a relative. We excluded MS patients with other neurological comorbid conditions, or with a relapse within 2 months before assessment. The MS treatment consisted of Natalizumab. The three kinds of drugs for transplant recipients were: Mycophenolate mofetil (10% of transplant recipients, *n* = 3), Cyclosporine plus Mycophenolate mofetil (29%; *n* = 9), or Tacrolimus plus Mycophenolate mofetil (61%; *n* = 19). Our Ethics and Health Research Commission approved this investigation, and written informed consent

was obtained from all participants. We used Spanish version of the SF-36 Health Survey (Alonso, Prieto, & Antó, 1995). Analysis of covariance was computed for each group to control for the time from MS diagnosis or transplantation surgery to assessment. Student *t* test for unpaired samples of covariate-adjusted mean values was used as statistical index, and Cohen's *d*s were calculated to assess the size of intergroup differences and the clinical significance between patients and a representative age-adjusted sample (18 to 64 years old) of the general Spanish population (n = 7881) (Alonso et al., 1998). Data were analyzed with IBM-SPSS 19.0 statistical software package (SPSS, Inc., Chicago, Ill) for Windows PC.

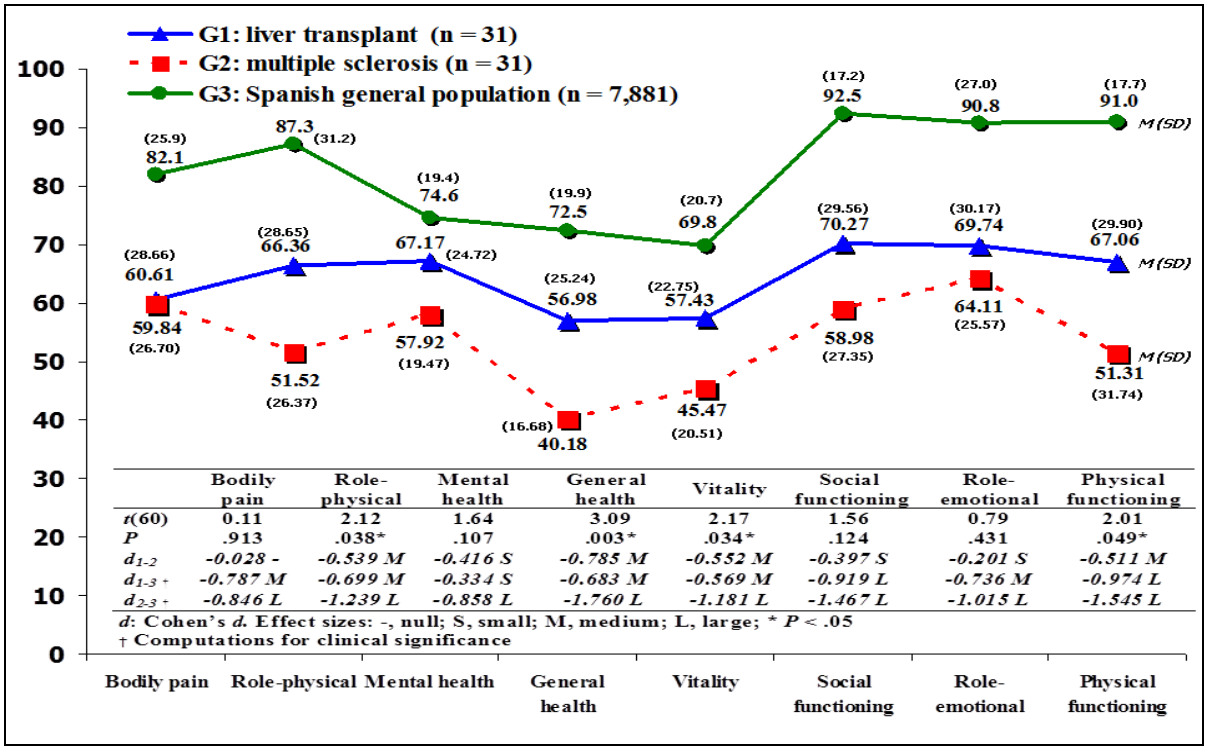
Results

We previously verified that no significant difference in the SF-36 subscales was related to immunosuppressants prescribed to transplant recipients: bodily-pain (F[2, 28] = 0.788, p = .465), role-physical (F[2, 28] = 0.175, p = .841), mental health (F[2, 28] = 0.250, p = .780), general health (F[2, 28] = 0.048, p = .953), vitality (F[2, 28] = 0.254, p = .778), social functioning (F[2, 28] = 1.001, p = .380), role-emotional (F[2, 28] = 0.110, p = .896), and physical functioning (F[2, 28] = 0.022, p = .978). Figure 1 shows significantly worse scores among neurological patients com- pared with liver transplant recipients regarding role-physical (p = .038), general health (p = .003), vitality (p = .034), and physical functioning (p = .049), with medium effect sizes (Cohen's *d*s from –0.511 to –0.785). Against normative values, liver transplant recipients achieved relevant differences in all SF-36 subscales (Cohen's *d*s from –0.569 to –0.974) except for mental health (Cohen's *d:* –0.334, small effect size). Likewise, MS patients showed much greater differences (Cohen's *d*s from –0.846 to –1.760) versus the reference group.

Discussion

This study sought to compare the QoL between two clinical groups controlling for the time from diagnosis/transplant surgery until the assessment because this variable has been reported to predict QoL (Aadahl, Hansen, Kirkegaard, & Groenvold, 2002; Guimaro et al., 2011; Jin et al., 2010). Relevant differences (large and medium effect sizes) were observed in both medical conditions against normative values. In line with other studies (Aadahl et al., 2002; Casetta et al., 2009), the scores were clinically

significant in most QoL domains: bodily pain; role and social activity limitations due to physical and emotional problems (role-physical, role- emotional, and social functioning); vitality; general health; as well as basic and instrumental activities of daily living (physical functioning). Only liver transplant recipients showed a level approaching that of the reference population in mental health as has been reported repeatedly (Aadahl et al., 2002; Jin et al., 2010). Regarding the comparison between patients, liver transplant recipients enjoyed better QoL than MS patients. The greatest differences were observed in the SF-36 physical subscales (role-physical, physical functioning, and vitality) due to the neurodegenerative nature of MS. Consistently, the neurological patients showed much worse self-perceived general health. Similarly, the self-perceptions of global health status showed coherence with other medical parameters in other studies (Casetta et al., 2009; Pérez-San-Gregorio, Martín-Rodríguez, Domínguez-Cabello, Fernández-Jiménez, & Bernardos-Rodríguez, 2013). We concluded that transplant recipients belong to a population that still requires special health care because, even after having undergone the treatment of choice to overcome their liver disease, they show clinically significant impairments in most major dimensions of biopsychosocial functioning.



	Bodily pain	Role-physical	Mental health	General health	Vitality	Social functioning	Role-emotional	Physical functioning
$t(60)$	0.11	2.12	1.64	3.09	2.17	1.56	0.79	2.01
P	.913	.038*	.107	.003*	.034*	.124	.431	.049*
d_{1-2}	-0.028 -	-0.539 M	-0.416 S	-0.785 M	-0.552 M	-0.397 S	-0.201 S	-0.511 M
d_{1-3} †	-0.787 M	-0.699 M	-0.334 S	-0.683 M	-0.569 M	-0.919 L	-0.736 M	-0.974 L
d_{2-3} †	-0.846 L	-1.239 L	-0.858 L	-1.760 L	-1.181 L	-1.467 L	-1.015 L	-1.545 L

d: Cohen's *d*. Effect sizes: -, null; S, small; M, medium; L, large; * $P < .05$
† Computations for clinical significance

Figure 1. Adjusted means on quality of life (SF-36) among liver transplantation and multiple sclerosis patients and means from the age-adjusted general Spanish population (the lower score, the worse quality of life).

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4.2. Segundo trabajo titulado "*Evolution of quality of life in renal transplant recipients and patients with multiple sclerosis: A follow-up study*"

Este trabajo corresponde al artículo publicado que se referencia a continuación:

Fernández-Jiménez, E., Pérez-San-Gregorio, M. A., Martín-Rodríguez, A., Pérez-Bernal, J., & Izquierdo, G. (2013). Evolution of quality of life in renal transplant recipients and patients with multiple sclerosis: A follow-up study. *Transplantation Proceedings*, *45*, 3616-3619.

Abstract

We aimed to compare the evolution of quality of life in two medical conditions under immunotherapy (cadaveric renal transplantation [G_1] and multiple sclerosis [G_2]), and to assess the clinical significance of the results compared with a representative age-adjusted sample of the general Spanish population (G_3). Using a mixed design (2x2), the SF-36 Health Survey was administered to 60 patients with one of these clinical conditions (30 in each group: the *patient group* factor), matched for gender, and homogenized regarding age and working status. All renal patients had undergone transplantation 6 months before the first assessment, and all neurological patients presented a relapsing-remitting course and a mild-moderate disability level. Both patient groups were assessed a second time 6 months later (the *phase* factor). A mixed analysis of covariance was computed controlling for age as a covariate. Cohen's *d* was reported as an effect size index and to analyze the clinical significance regarding a representative age-adjusted sample of the general Spanish population (n = 5821). Statistically significant differences were found between patient groups in vitality, bodily pain, social functioning, and mental health ($p < .01$), in which worse levels were displayed by patients with multiple sclerosis in both phases (Cohen's $ds_{1\text{-}2}$ from 0.61 to 1.40). Likewise, an interactive effect was observed in physical functioning [$F(1, 57) = 12.93$; $p = .001$], such that the performance of daily physical activities improved in renal recipients after 6 months, but it decreased in neurological patients. Patients with multiple sclerosis showed higher, clinically significant impairment in all SF-36 dimensions in both phases compared with renal recipients (Cohen's $ds_{2\text{-}3}$ from –0.50 to –1.61), who presented clinically significant impairment in general health, role-physical and role-emotional (Cohen's $ds_{1\text{-}3}$ from –0.73 to –1.28). Renal transplant recipients need specialized health care one year after transplantation because they still display relevant impairment in daily functioning compared with the general population.

Introduction

The comparison of quality of life (QoL) between renal transplant recipients and other patient populations would allow determination of the relative impact of these clinical conditions on QoL (Ingerski et al., 2010). Nevertheless, only a longitudinal study design would permit drawing more decisive conclusions than those from a cross-sectional study. This can be approached by two procedures: a) comparing renal to other organ transplant recipients, which has been widely performed (Pinson et al., 2000); or b) contrasting renal recipients with other chronic conditions unrelated to the transplantation process. This latter has scarcely been studied (Ingerski et al.) and would allow analyzing whether the impairments identified are due to the transplantation itself or to chronic condition-related stressors. Ideally, the other illness condition should share some similarities with the transplant group (e.g., its immunocompromised nature), hence multiple sclerosis (MS) is a suitable comparison condition (Fernández-Jiménez et al., 2012). This is the first study with the aims of comparing QoL evolution in two medical conditions under immunotherapy **(**cadaveric renal transplant recipients [G_1] and MS patients [G_2]**)**, and assessing the clinical significance of the results compared with a representative age-adjusted sample of the general Spanish population (G_3).

Methods

Selection and Description of Participants and Statistical Techniques

Sixty patients with one of these clinical conditions were assessed (30 patients in each group: the *patient group* factor), matched for gender (15 females in each group) and homogenized with regard to age ($mean_{G1}$ [M_{G1}] = 40.23 years, standard $deviation_{G1}$ [SD_{G1}] = 10.15 and M_{G2} = 39.57 years, SD_{G2} = 9.27; $F(1, 59) = 0.07$, $p = .791$) and working status [$\chi^2(2, 59) = 1.62$, $p = .444$]. The general inclusion criteria were as follows: a cognitive level allowing completion of the questionnaire, not having suffered a recent loss of a relative, and being treated with immunosuppressive drugs/immunomodulators. The specific exclusion criteria were as follows: hepato-renal and retransplantation cases, patients with MS with other comorbid neurological conditions, and an MS relapse during the 2 months prior to the assessment. The Spanish version of the SF-36 Health Survey was used. All renal patients had undergone transplantation 6 months before the first assessment phase, and all patients with MS presented a relapsing-remitting course and a mild-moderate disability level measured by

the Expanded Disability Status Scale (EDSS; from 1.0 to 5.5). Both patient groups were assessed a second time 6 months later (the *phase* factor). Our Research Ethics Commissions approved this investigation, and written informed consent was obtained from all participants. A mixed analysis of covariance (2x2 design) was computed, controlling for age as a covariate. Cohen's *d* was reported as an effect size index, as well as to analyze the clinical significance of the results regarding a representative age-adjusted sample (25 to 64 years old) of the general Spanish population (n = 5821) (Alonso et al., 1998). Data were analyzed with IBM-SPSS 19.0 statistical software package (SPSS, Inc., Chicago, Ill, United States) for Windows PC.

Results

Time since MS diagnosis (M = 108.03 months, SD = 82.20) was unrelated to any QoL subscale (Pearson's correlations [$rs_{Pearson}$] from –0.008 to .298). A main effect of the *patient group* factor was statistically significant in vitality, bodily pain, social functioning, and mental health (Table 1), in which worse levels were displayed by patients with MS compared with renal transplant recipients in both assessment phases (Cohen's $ds_{1\text{-}2}$ from 0.61 to 1.40). Likewise, a statistically significant interactive effect was observed in physical functioning [$F(1, 57) = 12.93$, $p = .001$; Table 2], such that the performance of daily physical activities improved in renal transplant patients after 6 months, but it decreased in patients with MS (Figure 1). However, the main effect of the *patient group* factor was greater in physical functioning [$F(1, 57) = 19.20$, $p = .000$] than the interactive effect, i.e., differences between clinical conditions were more relevant regardless of the study phase (Cohen's $ds_{1\text{-}2}$ = 0.76 and 1.32, in the first and second phase, respectively). No relevant differences were observed between time points regarding the remaining QoL dimensions in either patient group (null and small effect sizes). Patients with MS showed higher, clinically significant impairment in all QoL dimensions, in both phases (Cohen's $ds_{2\text{-}3}$ from –0.50 to –1.61), in comparison with renal transplant recipients, who reached normative levels in vitality, bodily pain and mental health in both assessment phases (Cohen's $ds_{1\text{-}3}$ from –0.09 to 0.14).

Table 1. Adjusted means of quality of life (SF-36) in renal transplant and patients with multiple sclerosis between time points, and clinical significance compared with the age-adjusted general Spanish population (lower scores represent worse quality of life).

	First phase					6 months later					Main effects		Interactive effects
SF-36 subscales	**Renal transplant M^*_{G1} (*SD*)**	**MS† patients M_{G2} (*SD*)**	**$d_{G1\text{-}G2}$‡**	**$d_{G1\text{-}G3}$**	**$d_{G2\text{-}G3}$**	**Renal transplant M_{G1} (*SD*)**	**MS patients M_{G2} (*SD*)**	**$d_{G1\text{-}G2}$**	**$d_{G1\text{-}G3}$**	**$d_{G2\text{-}G3}$**	**Group *F*(1, 57) (*p*)**	**Phase *F*(1, 57) (*p*)**	***F*(1, 57) (*p*)**
Role-physical	52.92 (30.39)	63.62 (30.39)	-0.35 S	-1.05 L	-0.71 M	59.19 (28.64)	59.35 (28.64)	-0.01 –	-0.87 L	-0.87 L	0.70 (.406)	0.59 (.448)	1.74 (.193)
Bodily pain	87.47 (25.32)	53.36 (25.32)	1.35 L	0.25 S	-1.06 L	83.58 (27.03)	57.09 (27.03)	0.98 L	0.10 –	-0.88 L	28.70 (.001)	0.60 (.443)	1.06 (.308)
General health	43.83 (22.13)	43.17 (22.13)	0.03 –	-1.28 L	-1.31 L	46.55 (19.90)	41.78 (19.90)	0.24 S	-1.21 L	-1.45 L	0.34 (.565)	0.34 (.565)	0.56 (.458)
Vitality	71.26 (22.45)	39.91 (22.45)	1.40 L	0.11 –	-1.33 L	67.02 (19.58)	44.98 (19.58)	1.13 L	-0.09 –	-1.17 L	35.49 (.001)	0.40 (.530)	2.28 (.136)
Social function	78.63 (26.95)	62.20 (26.95)	0.61 M	-0.59 M	-1.31 L	81.97 (29.53)	62.20 (29.53)	0.67 M	-0.41 S	-1.22 L	9.23 (.004)	0.01 (.912)	0.16 (.694)
Role-emotional	67.01 (32.03)	69.00 (32.03)	-0.06 –	-0.79 M	-0.72 M	69.18 (30.57)	67.10 (30.57)	0.07 –	-0.73 M	-0.81 L	0.00 (.995)	0.07 (.793)	0.18 (.675)
Mental health	78.31 (21.60)	59.55 (21.60)	0.87 L	0.20 S	-0.71 M	76.90 (19.91)	64.27 (19.91)	0.63 M	0.14 –	-0.50 M	11.88 (.001)	0.13 (.721)	1.17 (.284)

G_1: renal transplant; G_2: multiple sclerosis; G_3: general Spanish population.

*Means adjusted for age. †MS: multiple sclerosis. ‡Cohen's *d* index: –, null effect size; S, small effect size; M, medium effect size; L, large effect size.

Table 2. Simple effects regarding physical functioning (SF-36) in renal transplant and multiple sclerosis patients between time points, and clinical significance compared with the age-adjusted general Spanish population.

Physical functioning: Simple effects	***p***	$d_{G1\text{-}G2}$*	$d_{G1\text{-}G3}$	$d_{G2\text{-}G3}$
Renal transplant:	.026	-0.31 S		
- First phase				
- 6 months later				
Multiple sclerosis:	.007	0.38 S		
- First phase				
- 6 months later				
First phase:	.005	0.76 M	-0.51 M	-1.30 L
- Renal transplant				
- Multiple sclerosis				
6 months later:	.001	1.32 L	-0.16 –	-1.61 L
- Renal transplant				
- Multiple sclerosis				

Main effects		**Interactive effect**
Group ***F*(1, 57), *p***	**Phase** ***F*(1, 57), *p***	***F*(1, 57), *p***
19.20, *.001*	1.34, *.252*	12.93, *.001*

G_1: renal transplant; G_2: multiple sclerosis; G_3: general Spanish population. *Cohen's *d* index: –, null effect size; S, small effect size; M, medium effect size; L, large effect size.

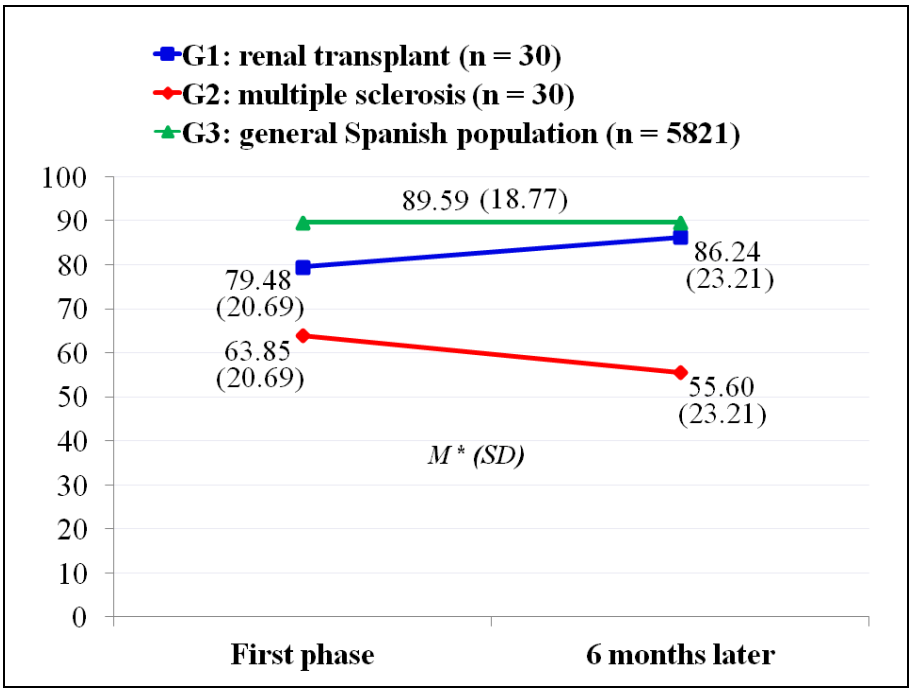

Figure 1. Adjusted means of physical functioning (SF-36) in renal transplant recipients and patients with MS between time points compared with mean of the age-adjusted general Spanish population (lower scores represent worse QoL). *Means adjusted for age (SD).

Discussion

Renal transplant recipients showed a better QoL, in terms of daily physical activities, vitality, pain, social functioning, and mental health, than patients with MS, at both 6 and 12 months after having undergone transplantation. Although patients with MS were in remission and they presented a mild-moderate disability level, their impairment was clinically significant in all QoL dimensions in both phases. Overall, both medical conditions retained similar levels of biopsychosocial functioning after 6 months (Pinson et al., 2000; Rebollo et al., 2003), although renal recipients presented a trend to improvement in basic and instrumental activities of daily living, reaching normative levels at that time. However, these renal recipients still showed clinically significant deterioration in terms of general health status and daily activity limitations due to physical and emotional problems. This latter impairment (role-emotional) contrasts with their nonclinical levels in negative affectivity (mental health subscale), which may be being amplified, thereby limiting their daily functioning, due to the interaction with other concurrent factors (e.g., demanding medical treatment). Thus, this population continues to require specialized health care one year after undergoing transplantation because they still show relevant difficulties in daily functioning due to their health problems, compared with the general population.

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4.3. Tercer trabajo titulado "*Psychometric properties of a revised Spanish 20-item Toronto Alexithymia Scale adaptation in multiple sclerosis patients*"

Este trabajo corresponde al artículo publicado que se referencia a continuación:

Fernández-Jiménez, E., Pérez-San-Gregorio, M. A., Taylor, G. J., Bagby, R. M., Ayearst, L. E., & Izquierdo, G. (2013). Psychometric properties of a revised Spanish 20-item Toronto Alexithymia Scale adaptation in multiple sclerosis patients. *International Journal of Clinical and Health Psychology*, *13*, 226−234.

Abstract

There have been a small number of investigations of alexithymia in multiple sclerosis (MS) using the 20-item Toronto Alexithymia Scale (TAS-20). However, the TAS-20 factor structure has not yet been evaluated in a MS patient sample, and earlier Spanish translations of this instrument require some improvement. We aimed to evaluate the factorial validity and reliability of an improved Spanish translation of the TAS-20 (the TAS-20-S). The TAS-20-S was completed by 221 MS patients. Confirmatory factor analysis was used to compare the fit of six different factor models. Internal consistency and retest reliability coefficients were also computed. The correlated three-factor model and the higher-order factor model made up of *Difficulty Identifying Feelings*, *Difficulty Describing Feelings*, and *Externally Oriented Thinking* achieved the best fit. Alpha coefficients ranged between .87 and .67; mean inter-item correlations ranged between .48 and .20; and retest correlations after 6 months ranged between .61 and .52. A high degree of alexithymia was present in 18.1% of the sample. Reliability and the traditional three-factor structure were demonstrated for the TAS-20-S, which can now be recommended for assessing an aspect of emotional processing in MS patients.

Introduction

Alexithymia is a multifaceted dimensional personality construct that reflects a disturbance in affective information processing and social-cognitive functioning (Taylor & Bagby, 2012; Wingbermühle, Theunissen, Verhoeven, Kessels, & Egger, 2012). This construct encompasses difficulties in identifying subjective feelings and differentiating between feelings and the somatic sensations associated with emotional arousal, difficulty verbalizing emotional feelings to others, a restricted imaginal capacity, and an externally- oriented style of thinking (Taylor, Bagby, & Parker, 1997). There may also be associated impairments in recognizing emotions in human facial expressions, as demonstrated in studies with healthy volunteers (Kano, Fukudo, & Gyoba, 2003) and multiple sclerosis patients (Prochnow et al., 2011).

Despite empirical evidence that alexithymia, and other related concepts, are associated with a wide variety of medical and psychopathological disorders and symptomatology (Balluerka, Aritzeta, Gorostiaga, Gartzia, & Soroa, 2013; Pascual,

Etxebarria, Cruz, & Echeburúa, 2011; Taylor & Bagby, 2012; Taylor et al., 1997), the construct has been scarcely investigated in multiple sclerosis (MS). This is somewhat surprising given recent findings that this personality trait is a strong predictor of the most quality-of-life disabling condition in MS, namely, depression (Bodini et al., 2008; Feinstein, 2011; Gay, Vrignaud, Garitte, & Meunier, 2010). The strong association between depression and alexithymia in MS might be explained partly by evidence that negative emotions are processed predominantly by neocortical areas in the right hemisphere (Adolphs, Jansari, & Tranel, 2001), which have been found to show reduced activation in response to emotional stimuli in individuals with high degrees of alexithymia (Kano et al., 2003), thereby contributing to deficits in the cognitive processing and regulation of negative affects.

The objectives of the few empirical studies that assessed alexithymia in MS patients were to identify the facets of the construct that are most relevant to MS (Bodini et al., 2008; Chahraoui et al., 2008; Gay et al., 2010), and to estimate the prevalence of alexithymia among MS patients, although the samples in these studies were small in size (58 to 115 patients). In pursuing these objectives, alexithymia was measured with the 20-item Toronto Alexithymia Scale (TAS-20) (Bagby, Parker, & Taylor, 1994), which is the most frequently and widely-used instrument for assessing the construct (Taylor & Bagby, 2012). This self-report scale is comprised of three factor scales that assess difficulty identifying feelings, difficulty describing feelings to others, and externally-oriented thinking. The TAS-20 has been translated into more than 24 different languages, and validated in clinical and/or nonclinical samples in Western, Eastern-European, East-Asian, and Middle-Eastern countries (Taylor & Bagby, 2012; Taylor, Bagby, & Parker, 2003).

To our knowledge, there are three existing Spanish adaptations of the TAS-20, two of which were developed in Latin-American countries – Mexico (Pérez-Rincón et al., 1997) and Peru (Loiselle & Cossette, 2001) – and one developed in Spain (Martínez-Sánchez, 1996; Páez et al., 1999). These adaptations of the scale have certain limitations. For example, the Mexican and Peruvian versions present some dialectical particularities when compared with the Spanish spoken in Spain. In addition, the Latin- American versions, and also the version developed in Spain,

contain some items whose back-translation does not adequately reflect the meanings of the original English version of the items. Moreover, the indices and criteria used to evaluate goodness of fit of the three-factor model of the Spanish translations of the TAS-20 do not meet the standards that are currently employed in psychometric studies and recommended in Hu and Bentler's (1999) guidelines.

Some investigators have obtained a different factor structure for the TAS-20 in studies with patient samples (Kooiman, Spinhoven, & Trijsburg, 2002; Müller, Bühner, & Ellgring, 2003; Pérez-Rincón et al., 1997), suggesting that the factor structure might depend on the specific sample analyzed. Although a few studies have used the TAS-20 to assess alexithymia in MS patients, the reliability and three- factor structure of the scale have not yet been evaluated in this population. It is important to address this deficiency not merely to satisfy professionals in the measurement field (Carretero-Dios & Pérez, 2007), but also for clinical reasons as evidence for the validity of the scale will allow researchers to identify which of the TAS-20 factor scales are differentially related to other clinical outcomes in a more meaningful way (Briggs & Cheek, 1986). There is evidence, for example, that the *Difficulty Identifying Feelings* factor scale of the TAS-20 is stronger than the total scale in predicting fatigue and depression in MS patients (Bodini et al., 2008).

Given the above considerations, the aim of this instrumental study (Montero & León, 2007) was to work collaboratively with the developers of the original English version of the TAS-20 to develop a revised and improved Spanish translation of the scale, and to evaluate its reliability and factor structure in a sample of patients with MS. This is the first study to assess alexithymia in a Spanish MS sample.

Method

Participants

Two hundred and sixty-five outpatients with MS who came for their routine medical checkups at the University Hospital Virgen Macarena in Seville, Spain, were invited to participate in this study in 2011. However, 44 patients were not enrolled because they declined (14 patients) or lacked time to participate (7 patients); or because of the following exclusion criteria: cognitive impairment (13 patients); neurological

comorbid conditions (5 patients); major psychiatric disorders (1 patient with chronic psychosis) or a significant mood disturbance at the time of assessment (2 patients); and other special conditions (2 patients pregnant). The final sample was comprised of 221 participants (83.4%), who were all diagnosed with multiple sclerosis according to the 2010 revised McDonald's criteria (Polman et al., 2011). The participants were involved through the convenience sampling technique. Sociodemographic data and information about the course of MS, functional disability according to the Expanded Disability Status Scale (EDSS), and pharmacotherapy were collected. The clinical and sociodemographic characteristics are presented in Table 1.

Instruments

The TAS-20 is a 20-item self-report instrument with each item scored on a 5-point Likert scale (Bagby et al., 1994). Total scores range between 20 and 100 with higher scores indicating greater degrees of alexithymia. The developers of the scale recommend the following empirically established cutoff scores: nonalexithymic cases: $\leq$ 51; borderline cases: 52-60; alexithymic cases: $\geq$ 61 (Taylor et al., 1997). The English version of the TAS-20 was adapted to the Spanish language in an iterative-process (Carretero-Dios & Pérez, 2005). First, the original English version was translated into Spanish by several university researchers in the field of clinical psychology, and with expertise in construction and adaptation of questionnaires, who also reviewed the existing Spanish adaptations of the TAS-20 and made corrections to items they thought had been inadequately translated. For example, a frequent mistake in translation was the use of "explain feelings" as a synonym for "describe feelings" when both verbs differentiate between a deeper emotional processing – analyze or explain – against a lighter one – describe –, and precisely the latter was the alexithymic characteristic of interest. Given the importance of reviewing the adequacy of a translation with statistical methods (Sireci, Yang, Harter, & Ehrlich, 2006), the new Spanish translation of the TAS-20 was also influenced by considering the inadequate psychometric functioning of some items in the earlier Spanish versions. Second, a Spanish-English bilingual PhD psychologist, who was familiar with the Spanish and American cultures but not given access to the original English version of the TAS-20, made a back-translation of the new Spanish translation. Finally, this back-translated English version was then reviewed and compared with the original English version by the developers of the TAS-20.

Moreover, a bilingual research assistant working in Canada also compared this back-translation with the Spanish version. Some further modifications were made until a consensus was reached about the final translation. The final Spanish adaptation of the scale (the TAS-20-S) was then pilot tested with 20 patients; the items were read to them to check if the items were correctly understood and to identify any difficulties in answering them. Only 8 items remained with the same or similar translation to the first version of the TAS-20 adapted in Spain.

Table 1. Clinical and sociodemographic characteristics of the multiple sclerosis patients (n = 221).

	Mean *(SD)*
Age (in years)	40.61 (9.65)
Months since diagnosis	101.43 (75.28)
Expanded Disability Status Scale (EDSS)	3.04 (1.83)
	% (*n*)
EDSS 0	4.10 (9)
Mild EDSS level (1-3.5)	61.50 (136)
Moderate EDSS level (4-6.5)	30.80 (68)
Severe EDSS level (> 7)	3.60 (8)
Multiple sclerosis course	
Relapsing remitting	77.80 (172)
Secondary progressive	17.70 (39)
Primary progressive	4.50 (10)
Disease modifying therapy: yes/no	76.90 / 23.1 (170 / 51)
Antidepressant medication: yes/no	27.10 / 72.9 (60 / 161)
Anxiolytic medication: yes/no	25.80 / 74.2 (57 / 164)
Female/male gender	63.03 / 36.7 (140 / 81)
Marital status	
Partner (married or stable relationship)	78.30 (173)
Single	14.09 (33)
Separated/divorced	5.90 (13)
Widow	0.90 (2)
*Educational level**	
High	549.50 (110)
Secondary	29.90 (66)
Primary	20.4 (45)
Employment status	
Permanent/transient disability	35.30 (78)
Working	34.40 (76)
Unemployed/students	15.4 (34)
Sick leave	7.20 (16)
Adapted work	2.30 (5)
Housewives	1.80 (4)
Retired	0.50 (1)

*High level: completed university or a high level vocational training program; Secondary level: completed high school or a medium level vocational training program; Primary level: did not complete high school. *Note*. SD = standard deviation.

Procedure

All patients were assessed individually by a trained psychologist (EFJ) during their routine checkups at the hospital after written informed consent was obtained. The TAS-20-S items were read by such psychologist, a method that has been used in other studies (Pérez-Rincón et al., 1997), given the MS patients' difficulties in understanding some of the items when they read the questionnaires by themselves. This procedure allowed us to avoid response tendencies and the problems with negatively-worded items reported in other studies (Loiselle & Cossette, 2001). The writing of this manuscript has followed the Hartley's (2012) guidelines. The study was approved by the Ethics Commission of Research of the University Hospital Virgen Macarena.

Data analysis

Confirmatory factor analyses were conducted using the matrix of polychoric correlations, as was carried out in other studies (Gorostiaga, Balluerka, Aritzeta, Haranburu, & Alonso-Arbiol, 2011), with Weighted Least Squares Means and Variances (WLSMV) estimation (Flora, LaBrish, & Chalmers, 2012). The goodness-of-fit indices computed and presented according to Hammervold and Olsson's (2012) classification were as follows: chi-square goodness-of-fit index; Weighted Root Mean Square Residual (WRMR) was selected as a measure of *absolute fit* and *residual-based fit*; the Tucker–Lewis Index (TLI) and the Comparative Fit Index (CFI) were selected as measures of *incremental fit*; and the Root-Mean-Square Error of Approximation (RMSEA) along with its 90% confidence interval was chosen as a measure of *parsimonious fit*. All these indices were interpreted simultaneously to overcome the limitations of each one (Carretero-Dios & Pérez, 2005; Hammervold & Olsson, 2012). The following standards were used to assess the model fit: a non-significant value of chi-square; WRMR ≤ 1 (Yu, 2002); TLI and CFI $\geq .90$ (Marsh, Hau, & Wen, 2004); and RMSEA $< .08$ (MacCallum, Browne, & Sugawara, 1996). Each of the TAS-20 items was specified as an indicator of only a single factor.

The following six different factor models were tested and compared:

1) A unidimensional model in which all items load on one unique factor (Lambert et

al., 1999).

2) An oblique two-factor model in which *Difficulty Identifying Feelings* (DIF) and *Difficulty Describing Feelings* (DDF) belong to the same factor (DIDF) and *Externally Oriented Thinking* (EOT) is isolated in another factor (Kooiman et al., 2002; Pérez-Rincón et al., 1997).

3a) The traditional oblique three-factor model made up of DIF, DDF and EOT, according to the developers of the TAS-20 (Bagby et al., 1994).

3b) A comparable hierarchical model was also tested in which DIF, DDF, and EOT were specified to indicate a second-order factor: *Global Alexithymia*.

3c) An alternative oblique three-factor model with DIF and DDF belonging to the same factor (DIDF); and EOT divided into two separate factors: *Pragmatic Thinking* (PR) – items 5, 8 and 20 – and *Lack of Importance of Emotions* (IM) – items 10, 15, 16, 18, and 19 (Müller et al., 2003).

4) An oblique four-factor model with DIF, DDF, PR and IM as separate factors (Müller et al., 2003).

To assess internal consistency reliability of the TAS-20-S, alpha coefficients and mean inter-item correlations (MICs) were computed for the best fitting factor model. A standard of .70 or higher was set for alpha coefficients and an optimal range of .20 to .40 for MICs (Briggs & Cheek, 1986). Finally, 85 of the participants were enrolled to evaluate retest reliability; these patients completed the TAS-20-S approximately 6 months (M = 5.70 months, SD = 0.99) after its initial administration. No missing data were found and no data transformations were carried out. All analyses were conducted with the program Mplus 6.1 (Muthén & Muthén, 2011) and the IBM-SPSS 19.0 statistical software package (SPSS, Inc., Chicago, Ill) for Windows PC.

Results

No statistically significant differences were found between the participants in the

study and the nonparticipants (n = 44) in the variables of age [$F_{(1, 263)}$ = 0.118, p = .731] , gender [$\chi^2_{(1, 265)}$ = 0.104, p = .747], EDSS [$F_{(1, 53.711)}$ = 2.895, p = .095], and number of months since MS diagnosis [$F_{(1, 263)}$ = 0.473, p = .492].

In the participant sample, the mean total TAS-20-S score was 46.68 (SD = 14.38); alexithymic cases: 18.1% of sample (n = 40), mean 68.15 (SD = 5.24); borderline cases: 20.4% of sample (n = 45), mean 57.09 (SD = 2.73); nonalexithymic cases: 61.5% of sample (n = 136), mean 36.92 (SD = 7.63).

Confirmatory factor analysis

Factor loadings for each item across models are presented in Table 2. All items demonstrated statistically significant substantial loadings (≥ .30) on their specified factor across models, with the exception of model 1. In model 1, items 19, 15, 10, 5 and 16 failed to reach this minimal loading value. Correlations among factors across models are reported in Table 3. Correlations among factors were all moderate to large in size, ranging from .29 to .82. Based on the goodness-of-fit statistics evaluated (see Table 4), models 3a, 3b, and 4 achieved reasonable model fit. However, the specified higher-order model (3b) resulted in a small non-significant negative residual variance for DDF. Fixing this value to zero (resulting in a factor loading of 1.00) resulted in a reasonably fitting model that is nearly identical to the standard three-factor model (3a). All first- order coefficients were positive and statistically significant in this case, and the second-order factor loadings for DIF and EOT were .79 and .56, respectively (all p < .001). Model 4 demonstrated a slightly better fit than models 3a and 3b; however, the correlation > 1.0 between IM and PR (also found in model 3c) is an indication that the two factors are not statistically distinguishable, making the results of this model inadmissible. Overall, the standardized factor loadings from the traditional three-factor model (3a) were higher in the current study in comparison to those from the previous Spanish version of the TAS-20.

Reliability

Table 5 shows the MICs and alpha coefficients for the total TAS-20-S and three factor scales for the traditional three- factor model (3a). The MICs for the total scale and the DDF and EOT factor scales are in the recommended range of .20 to .40, indicating

adequate item-to-scale homogeneity. Although the MIC for the DIF factor scale is outside this optimal range, it is between .10 and .50, which is considered acceptable. The alpha coefficients range between .72 and .86 for the full scale and DIF and DDF factor scales, but for EOT the alpha coefficient is below the criterion of .70. The retest correlations for the full scale and three factor scales are all significant.

Table 2. Standardized factor loadings for each model.

	Model 1	**Model 2**		**Model 3a**			**Model 3c**			**Model 4**			
Item		*DIDF*	*EOT*	*DIF*	*DDF*	*EOT*	*DIDF*	*PR*	*IM*	*DIF*	*DDF*	*PR*	*IM*
1	.853	.857		.872			.857			.872			
3	.548	.554		.571			.555			.574			
6	.806	.812		.824			.812			.825			
7	.684	.692		.711			.692			.710			
9	.832	.838		.855			.838			.855			
13	.731	.738		.757			.738			.755			
14	.730	.735		.751			.736			.751			
2	.793	.799			.877		.799				.876		
4	.617	.623			.665		.622				.666		
11	.597	.601			.648		.600				.648		
12	.420	.419			.456		.418				.456		
17	.564	.563			.616		.562				.615		
5	.263		.454			.446		.418				.417	
8	.469		.710			.698		.650				.651	
10	.237		.459			.464			.497				.497
15	.207		.339			.348			.364				.369
16	.287		.463			.459			.488				.469
18	.391		.528			.543			.548				.559
19	.195		.405			.416			.444				.454
20	.406		.640			.634		.593				.593	

Note. DIDF = Difficulty Identifying Feelings together with Difficulty Describing Feelings; DIF = Difficulty Identifying Feelings; DDF = Difficulty Describing Feelings; EOT = Externally Oriented Thinking; PR = Pragmatic Thinking; IM = Lack of Importance of Emotions. All factor loadings are statistically significant, $p < .001$.

TABLE 3. Correlations among the factors.

	Model 2	**Model 3a**		**Model 3c**		**Model 4**		
	EOT	*DDF*	*EOT*	*PR*	*IM*	*DDF*	*PR*	*IM*
DIDF	.50			.58	.43			
DIF		.82	.41			.82	.54	.29
DDF			.61				.59	.63
EOT								
PR					1.04			1.03

Note. DIF = Difficulty Identifying Feelings; DDF = Difficulty Describing Feelings; EOT = Externally Oriented Thinking; PR = Pragmatic Thinking; IM = Lack of Importance of Emotions. All correlations are statistically significant, $p < .001$.

TABLE 4. Goodness-of-fit indices of the factor models.

	1	*2*	*3a*	*3b*	*3c*	*4*
X^2	599.683	440.767	388.316	388.821	437.819	370.562
df	170	169	167	168	167	164
p	< .001	< .001	< .001	< .001	< .001	< .001
RMSEA	.107	.085	.077	.077	.086	.075
90% confidence	.098 - .116	.076 - .095	.067 - .088	.067 - .087	.076 - .096	.065 - .086
CFI	.864	.914	.930	.930	.914	.935
TLI	.848	.904	.920	.921	.903	.924
WRMR	1.483	1.268	1.169	1.174	1.259	1.133

Note. RMSEA = Root Mean Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker Lewis Index; WRMR = Weighted Root Mean Square Residual.

TABLE 5. Alpha coefficients and mean inter-item correlations (MIC) for the TAS-20-S and its factor scales (model 3a).

Factor scales	*Cronbach's α*	*MIC*	*Retest reliability*
DIF	.87	.48	r = .52, p < .001
DDF	.72	.34	r = .61, p < .001
EOT	.67	.20	r = .56, p < .001
TAS-20-S total	.86	.22	r = .57, p < .001

Note. DIF = Difficulty Identifying Feelings; DDF = Difficulty Describing Feelings; EOT = Externally Oriented Thinking.

Discussion

In this pioneering study with a multiple sclerosis patient sample, our objectives were: a) to evaluate the factor structure of an improved Spanish translation of the TAS-20, which we named the TAS-20-S; and b) to evaluate the reliability of the TAS-20-S and its factor scales.

Regarding the first objective, the three-factor model of the TAS-20 was confirmed in the Spanish multiple sclerosis patient sample. The traditional correlated three-factor model and a higher-order factor model were the best fitting, both showing comparable results. Therefore, the factor scales Difficulty Identifying Feelings, Difficulty Describing Feelings, and Externally Oriented Thinking were replicated as core facets of the alexithymia construct assessed by the TAS-20 (Taylor et al., 2003). Although the use of externally imposed cutoff values to assess the goodness of fit of a model has been questioned – e.g., because the widely used Hu and Bentler's (1999) guidelines have

sometimes been misinterpreted and considered too demanding – (Marsh et al., 2004), in the current study most goodness-of-fit indices for both three-factor models (3a and 3b) were adequate and acceptable. However, WRMR values were slightly above the criterion level of ≤ 1, and the chi-square goodness of fit was significant for all models. Although the four-factor model showed a slightly better fit, two factors (PR and IM) were statistically indistinguishable (correlation > 1). Therefore, the differentiation of the EOT factor into two separate factor scales was not justified in this sample in contrast to results obtained in some studies conducted with samples of patients with other diagnoses (Müller et al., 2003).

The current study included the recommended incremental fit indices (TLI and CFI), which were not computed in earlier confirmatory factor analytic studies of Spanish adaptations of the TAS-20 (Loiselle & Cossette, 2001; Páez et al., 1999). These indices are currently regarded as essential for assessing goodness of fit (Hu & Bentler, 1999) because TLI and CFI are relatively unaffected by sample size, and both detect model misspecification (Jackson, Gillaspy, & Purc-Stephenson, 2009). Although the CFI and TLI values in the MS patient sample did not reach the level of ≥ .95, which is considered acceptable according to Hu and Bentler's (1999) demanding guidelines, relaxing the criterion standard to ≥ .90 resulted in these fit indices indicating an adequate fit (Marsh et al., 2004). Moreover, the TLI and CFI values obtained in the current study exceed values reported in earlier studies for Dutch, Italian, Japanese, and Mandarin translations of the TAS-20 (Taylor et al., 2003; Zhu et al., 2007).

As was found when an improved Greek adaptation of the TAS-20 was developed (Tsaousis et al., 2010), the values of the goodness-of-fit indices for the TAS-20-S were better than those reported for earlier Spanish versions of the scale (Páez et al., 1999), and also supported the traditional three-factor model rather than a two-factor model (Pérez- Rincón et al., 1997). Moreover, regarding the three-factor model 3a, the factor loadings of 10 of the 12 items modified were higher in the current revised Spanish version in comparison to the first Spanish version of the TAS-20 administered to samples in Spain and Mexico (Martínez- Sánchez, 1996; Páez et al., 1999). This is consistent with other studies showing that the use of both judgmental and statistical techniques to ensure item comparability across languages can improve the

psychometric properties of psychological measures (Sireci et al., 2006).

The estimates of internal consistency reliability were good for the total TAS-20-S and for the DIF and DDF factor scales, with particularly high alpha coefficients for DIF and the total scale. Although the alpha coefficient for the EOT factor scale was below the recommended standard of .70, and questionable according to George and Mallery (2003), the total scale and the DDF and EOT factor scales were within the optimal range of .20 to .40 for the mean inter-item correlations (MICs), which is a more appropriate index of a scale's cohesiveness (Briggs & Cheek, 1986).

Moreover, the alpha coefficient for EOT was higher than has been reported for most other language adaptations of the TAS-20 (Taylor et al., 2003; Tsaousis et al., 2010; Zhu et al., 2007). Although the MIC for the DIF factor scale was outside the optimal range, it was less than .50, which is considered acceptable for multifactor scales (Briggs & Cheek, 1986). Thus all three factor scales of the TAS-20-S can be considered homogeneous, and can be scored along with the TAS-20-S total score in studies with MS populations.

Although retest reliability of the TAS-20-S was demonstrated over a 6-month interval, the correlations were lower in magnitude than those reported in other studies with medical patient samples and with a similar time interval between assessments. For example, the retest correlation of the total TAS-20 was .66 in a sample of women with breast cancer after a 6-month follow-up (Luminet, Rokbani, Ogez, & Jadoulle, 2007). The lower temporal stability of the TAS-20-S in the current study may possibly be accounted for by the neurodegenerative nature and variable course of MS.

The prevalence of alexithymic cases in this larger MS sample than previously investigated was 18.1% and 20.4% for borderline cases, which is in the range found in two other studies with MS patients – 13.8% in Italy (Bodini et al., 2008) and 23.2% in France (Gay et al., 2010) – using the same cut-off points. The prevalence rates of alexithymia are similar to the prevalence rates of depression in MS (Wood et al., 2013); hence the problems in emotional processing are not negligible in MS and neuropsychological interventions to address these impairments are required

(Wingbermühle et al., 2012). Other research with various clinical populations has shown that treatments aimed at reducing alexithymia can result in better biopsychosocial outcomes (Beresnevaité, 2000; Melin, Thulesius, & Persson, 2010; Tulipani et al., 2010).

In conclusion, the results of the current study support the factorial validity of the TAS-20-S and indicate that it is a reliable instrument that can be used to assess an important aspect of emotional processing in MS populations. In particular, the scale might be used to investigate the clinical relevance of each of the three facets of the alexithymia construct in MS that may suggest a need for specific treatment interventions. Further research is needed to evaluate the psychometric properties of the TAS-20-S in community and other clinical samples, including assessment of the convergent and discriminant validity of the scale.

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4.4. Cuarto trabajo titulado "*A relative importance analysis of alexithymia and negative affect on pain intensity and pain interference in multiple sclerosis: An 18-month follow-up study*"

Abstract

The relative importance of alexithymia and negative affect in predicting pain outcomes has never been examined using the accurate statistical procedure. In the present study, the differential predictive value of these affective variables was longitudinally studied in a sample of patients with multiple sclerosis. From an 18-month follow-up design (baseline –T1–, 6 months –T2–, and 18 months –T3– after baseline), alexithymia (Toronto Alexithymia Scale, TAS-20), negative affect (SF-36 Mental health), and sociodemographic variables (age, gender and years of education) were jointly considered to predict several pain outcomes through a statistical procedure based on relative weights, where the measurement error was also taken into account. Two hundred and eleven patients with multiple sclerosis also completed the SF-36 Bodily pain (at T1, T2 and T3) and the Brief Pain Inventory subscales (at T3) regarding pain intensity (average, the strongest and the mildest one) and functional interference due to pain. Negative affect consistently predicted all the pain outcomes in almost all the models, such that lower levels of Mental health were related to greater pain intensity and pain interference at all three measurement points. The TAS-20 Difficulty Identifying Feelings subscale predicted Bodily pain at T3 and Pain interference, indicating that the greater emotional confusion, the greater pain intensity greater and functional interferences due to pain 18 months after baseline. This alexithymic dimension was not statistically different from negative affect in any of these two models. In conclusion, when several predictors were jointly considered, a major factor to explain pain, namely anxious-depressive symptomatology, was not proven to be more relevant than Difficulty Identifying Feelings in longitudinally predicting some parameters of pain.

Introduction

Pain in people with multiple sclerosis (PwMS) is a very frequent and disabling symptom. Specifically, according to meta-analysis, the prevalence of overall pain in this population is 62.8% [95% confidence interval (CI) 55.1 – 70.3%] (Foley et al., 2013), and this is associated with impairment in their biopsychosocial functioning (Hadjimichael, Kerns, Rizzo, Cutter, & Vollmer, 2007; O'Connor, Schwid, Herrmann, Markman, & Dworkin, 2008; Svendsen, Jensen, Hansen, & Bach, 2005).

Further, meta-analytic findings show that neuropathic pain is more prevalent than the nociceptive forms in PwMS (Foley et al., 2013). Hence, research in MS has focused on which factors trigger and maintain several parameters of pain despite absence of nociceptor stimulation.

Several factors have been identified as predictors of pain outcomes in PwMS, be they sociodemographic, disease-related, or psychological (O'Connor et al., 2008). In the current study, affective variables, namely negative affect and, above all, alexithymia, will be highlighted.

The association between pain and state-dependent affective variables, such as anxious-depressive symptomatology, has received considerable scientific attention in MS literature (Alschuler, Ehde, & Jensen, 2013; Huber, Suman, Biasi, & Carli, 2009; O'Connor et al., 2008). However, one of the constructs closely associated with negative affect, i.e., alexithymia (Marchesi, Bertoni, Cantoni, & Maggini, 2008; Marchesi et al., 2014), has been widely related to pain in several medical conditions (Glaros & Lumley, 2005; Hosoi et al., 2010; Huber et al., 2009; Kojima, 2012; Makino et al., 2013; Mehling & Krause, 2005; Porcelli, Tulipani, Maiello, Cilenti, & Todarello, 2007), but it has hardly been studied in PwMS. In fact, just one research work analyzed the relationship between alexithymia and pain in MS, but this mainly focused on a single pain type such as migraine (Villani, Prosperini, Pozzilli, Salvetti, & Sette, 2011).

Because of the close association between negative affect and alexithymia, several works have studied their potential overlap, concluding that they are highly related but independent (Hintikka, Honkalampi, Lehtonen, & Viinamaki, 2001; Marchesi,

Brusamonti, & Maggini, 2000). In the same line, this possible construct redundancy has been addressed by jointly analyzing the role of negative affect and alexithymia in predicting pain outcomes (Glaros & Lumley, 2005; Hosoi et al., 2010; Huber et al., 2009; Makino et al., 2013; Saariaho, Saariaho, Mattila, Karukivi, & Joukamaa, 2013; Sipila et al., 2001).

Nonetheless, the earlier studies addressing this issue were characterized by the following three shortcomings. First, correlation-based statistical procedures were used (including regression models), which discard the actual correlation between these two affective constructs, as if the everyday psychological functioning of PwMS were comprised of separate factors (Tonidandel, Lebreton, & Johnson, 2009). In this sense, it has been stated that partial correlations and standardized regression coefficients analyze the weight of a predictor by artificially holding the remaining variables constant (Kraha, Turner, Nimon, Zientek, & Henson, 2012). Second, these studies did not take into account the inevitable measurement error that every observed measure presents to some degree. Third, the previous studies used a cross-sectional design, so that longitudinal works about the contribution of affective variables in the development of pain in MS are needed (O'Connor et al., 2008).

Given the above-mentioned limitations, further research is required in order to ascertain the differential predictive value of alexithymia and negative affect on pain outcomes in PwMS over time. In the current study, an innovative statistical procedure based on relative weights will be used. According to Johnson's (2000) model, these indexes consider each predictor both orthogonally and jointly regarding the remaining variables with which it is correlated. Also, these indexes can be statistically compared to each other (Tonidandel & LeBreton, 2011; Tonidandel et al., 2009).

In the present 18-month follow-up study (baseline, 6 and 18 months after baseline), we aimed to longitudinally analyze the relative importance of alexithymia and negative affect on pain intensity and pain interference in PwMS, taking into account relevant sociodemographic variables and measurement error.

Methods

Participants

Two hundred and sixty-four outpatients with MS who came for their routine medical checkups at the University Hospital Virgen Macarena in Seville, Spain, were invited to participate in this study in 2011. However, 45 patients were not enrolled in any phase of the study because they declined (14 patients), lacked time to participate (7 patients); or because of the following exclusion criteria: cognitive impairment (13 patients); neurological comorbid conditions (4 patients); major psychiatric disorders (1 patient with psychosis and 1 patient with bipolar disorder); a significant mood disturbance at the time of assessment (2 patients); and other special conditions (2 patients were pregnant and 1 patient was breastfeeding). Likewise, 8 patients only participated at baseline but they declined or lacked time to continue in the following two phases of the current study. The final sample comprised 211 participants (79.9%) at baseline (T1), of whom 200 participated a second time (T2) and 201 were assessed a third time (T3) –11 patients differed between T2 and T3. The participants were all diagnosed with multiple sclerosis according to the 2010 revised McDonald's criteria (Polman et al., 2011) and were recruited through the convenience sampling technique. The entire sample comprised 132 females (62.6%) and presented a mean age of 40.52 (*SD* = 9.62) at T1. The remaining sociodemographic and disease-related variables of the entire sample at T1 are shown in Table 1. A more exhaustive assessment of pain was carried out at T3. In particular, regarding the pain site, 113 patients (56.2% of the sample at T3) reported several painful areas, headache was found in 24 (11.9%), no pain in 17 (8.5%), pain in legs in 14 (7%), upper back/neck in 8 (4%), middle-low back in 7 (3.5%), knees in 3 (1.5%), feet in 3 (1.5%), arms in 3 (1.5%), and other pain sites in 9 patients (4.5%). Furthermore, 41.8% (84 patients) of the entire sample took one painkiller at T3, 22.9% (46) reported taking 2 painkillers, 13.9% (28) did not take any drugs, 9.5% (19) reported 3 painkillers, 9% (18) reported 4 painkillers, 1.5% (3) reported 5, 1% (2) reported 6 and 0.5% (1 patient) of the sample reported taking 8 painkillers at T3.

Table 1. Sociodemographic and disease-related variables of the entire sample at T1 (*n* = 211).

	Mean (*SD*) [a]
Education (years)	12.89 (4.01)
Time since diagnosis (months)	100.78 (75.75)
Expanded Disability Status Scale (EDSS)	3.03 (1.80)
	% (*n*)
EDSS 0	3.8 (8)
Mild EDSS level (1 – 3.5)	62.1 (131)
Moderate EDSS level (4 – 6.5)	30.3 (64)
Severe EDSS level (≥ 7)	3.8 (8)
Multiple sclerosis course	
Relapsing remitting	78.2 (165)
Secondary progressive	17.5 (37)
Primary progressive	4.3 (9)
Disease modifying therapy: yes/no	76.8 / 22.3 (162 / 47) [b]
Antidepressant medication: yes/no	27.5 / 72.5 (58 / 153)
Anxiolytic medication: yes/no	25.1 / 74.9 (53 / 158)
Marital status	
Partner (married or stable relationship)	78.2 (165)
Single	14.7 (31)
Separated/divorced	6.2 (13)
Widow	0.9 (2)
Employment status	
Permanent/transient disability	44.1 (93)
Working	34.6 (73)
Unemployed/students	9 (19)
Sick leave	7.6 (16)
Adapted work	2.4 (5)
Homemaker	1.9 (4)
Retired	0.5 (1)

[a] SD = standard deviation. [b] Sample size equals to 209 patients because two of them were participating in a clinical study and did not know if they were receiving the active ingredient or the placebo.

Measures

Disability. The Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) was chosen to measure the degree of neurological impairment of the patients. It ranges from 0 to 10, with higher scores indicating more severe disability levels. The physician-administered form was used.

Alexithymia. Alexithymia was assessed using the 20-Item Toronto Alexithymia Scale (Bagby, Parker, & Taylor, 1994). A new Spanish version (the TAS-20-S) has recently been validated in MS population (Fernández-Jiménez et al., 2013), and the same factor structure as the original English version was confirmed with the following subscales: *Difficulty Identifying Feelings* (DIF), *Difficulty Describing Feelings* (DDF), and *Externally Oriented Thinking* (EOT). A total score can also be computed. For all the

scores (total or subscale scores), a higher score indicates greater degree of alexithymia. Following the guidelines of George and Mallory (George & Mallery, 2003), in the present study the coefficients of internal consistency ranged from good (TAS-20 total score: .853; DIF: .863), acceptable (DDF: .719) to questionable (EOT: .663).

Negative affect. Mental health from the SF-36 Health Survey (Ware & Sherbourne, 1992) was considered as a proxy of negative affect. The Spanish version was administered (Alonso, Prieto, & Antó, 1995). In this subscale, a higher score indicates less negative affect. In the current study, the internal consistency coefficient was good (.875).

Pain measures.

The Bodily pain subscale from the SF-36 Health Survey was chosen. It assesses pain intensity and interference with usual work during the month prior to the assessment. In this subscale, a higher score indicates less pain. In the present sample, Cronbach's alpha over time was good (T1: .886; T2: .877; and at T3: .880).

Moreover, pain intensity and pain interference were assessed using the Brief Pain Inventory (BPI) (Daut, Cleeland, & Flanery, 1983). The Spanish version was administered (Badia et al., 2003). Both dimensions were measured using a 0–10 numerical rating scale (Cleeland & Ryan, 1994), ranging from "no pain/does not interfere" (0) to "pain as bad as it could be/completely interferes" (10), referring to the past seven days. Regarding intensity, participants were asked to rate the average, the strongest and the mildest intensity of their pain. Regarding interference, participants were asked the extent to which their pain interfered with general activity, mood, walking ability, normal work, relationships with other people, sleep and enjoyment of life. As in previous works (Hosoi et al., 2010), "walking ability" was combined with "ability to get around", so that participants who do not walk due to their disability could respond to the item. The criterion variable of pain interference was the averaged score of these seven items, and its internal consistency coefficient was excellent (.948) in the current sample. For both dimensions, higher scores are related to higher pain intensity and more functional interference due to pain.

Procedures

Participants were individually assessed three times: at baseline (T1), 6 months later (T2) and 18 months from baseline (T3). All patients were evaluated face-to-face at T1 by a trained psychologist (EFJ) during their routine checkups at the hospital, after written informed consent was obtained. All the questionnaires were read aloud by this psychologist in order to avoid the PwMS' difficulties to understand items when they read the questionnaires by themselves. The assessment protocol at T2 and T3 was administered face-to-face at the hospital or conducted over the telephone, in both cases, by the same psychologist (EFJ). Bodily pain from the SF-36 Health Survey was administered at T1, T2 and T3. The pain intensity and pain interference items from the BPI were only asked at T3. The EDSS score was obtained from the hospital dataset. The study was approved by the Ethics Committee of Research of the University Hospital Virgen Macarena.

Data analyses

All the relative weight analyses were performed using the *Fitting and Interpreting multiple REgression* (FIRE) (Lorenzo-Seva & Ferrando, 2011) macro in SPSS version 20. This program is based on Johnson's relative weights (Tonidandel et al., 2009) in order to identify the strongest predictors of the criterion variables. FIRE presents several advantages compared with other statistical software which also compute relative weights: a) it indicates whether a relative weight is statistically different from zero by comparing the relative weight of the predictor with that of a variable unrelated (random) to the criterion (Tonidandel et al., 2009); b) it compares the statistical significance among predictors (pairwise comparisons); and c) it enables taking into account the measurement error of every questionnaire, so that coefficients of internal consistency for each scale were entered in the present study. FIRE computes relative weights reported as percentages, such that these indicate the variance proportion of the entire model that is accounted for by a specific predictor (Tonidandel et al., 2009). All the models included the same predictors: age, gender, years of education, Mental health and the respective score from the TAS-20 (total or subscale scores, one per model). The sociodemographic variables chosen were those which correlated with the criterion variables in preliminary analyses, as well as those identified in the literature as predictors of pain (Hadjimichael et al., 2007; O'Connor et al., 2008). All the predictors

belonged to the baseline of the study. Although FIRE enables splitting the dataset to cross-validate results, this option was not chosen so as not to lose statistical power (Lorenzo-Seva & Ferrando, 2011). Moreover, beta weights and structure coefficients were reported. For all statistical indexes, their respective 95% confidence intervals were computed across 10,000 bootstrapped samples (Baguley, 2009). The inclusion of zero value within these intervals indicates that beta weights and structure coefficients are statistically significant. Also, the unpaired samples *t*-test (for equal or unequal variances, accordingly), Pearson's Chi-square test, zero-order and partial correlations were computed when appropriate.

Results

No statistically significant differences were found between the participants in the study and the nonparticipants (n = 53) in the variables of age: $t(262) = -0.21$, $p = .835$; gender: $\chi^2(1, 264) = 0.527$, $p = .468$; EDSS: $t(67.81) = -1.73$, $p = .088$; or months since MS diagnosis: $t(262) = 0.32$, $p = .747$.

Means (SD) of affective and pain measures are presented in Table 2. Multicolinearity tests yielded values ranging from .675 to .995 for Tolerance and from 1.005 to 1.481 for Variance Inflation Factor, indicating the correlation between predictors could be handled appropriately by relative weight indexes (Tonidandel & LeBreton, 2011).

Table 2. Means (*SD*) of affective and pain measures.

Affective measures	***M* (*SD*)** [a]	**Pain measures**	***M* (*SD*)**
SF-36 Health Survey [b]		*SF-36 Health Survey*	
Mental health	60.09 (21.98)	Bodily pain at T1	59.27 (31.33)
		Bodily pain at T2	62.70 (32.02)
		Bodily pain at T3	55.12 (29.20)
TAS-20 [c]		*BPI* [h]	
DIF [d]	16.18 (7.53)	Average intensity	4 (2.59)
DDF [e]	13.06 (5.20)	Strongest intensity	5.61 (3.02)
EOT [f]	18.08 (5.43)	Mildest intensity	1.96 (1.90)
Total score [g]	47.32 (14.27)	Pain interference	3.23 (2.93)

[a] *SD* = standard deviation. [b] Scores can range from 0 to 100. [c] The Toronto Alexithymia Scale. [d] DIF = Toronto Alexithymia Scale Difficulty Identifying Feelings subscale. [e] DDF = Toronto Alexithymia Scale Difficulty Describing Feelings subscale. [f] EOT = Toronto Alexithymia Scale Externally Oriented Thinking subscale. [g] Scores can range from 20 to 100. [h] Scores can range from 0 to 10 in each Brief Pain Inventory measure.

Table 3. Zero-order correlations between negative affect and pain measures.

Study stage	Pain measures	Mental health [d] *r* (*p*)	Study stage	Pain measures	Mental health *r* (*p*)
Baseline [a]	Bodily pain [c]	.506 (.000)	**Time 3** [e]	Bodily pain	.460 (.000)
				Average intensity [f]	-.384 (.000)
				Strongest intensity [f]	-.380 (.000)
Time 2 [b]	Bodily pain	.456 (.000)		Mildest intensity [f]	-.411 (.000)
				Pain interference [f]	-.501 (.000)

[a] *n* = 211 patients. [b] *n* = 200 patients. [c] This subscale belongs to the SF-36 Health Survey. [d] This subscale belongs to the SF-36 Health Survey and is a proxy of negative affect. [e] *n* = 201 patients. [f] These measures belong to the Brief Pain Inventory.

Preliminary analyses: zero-order correlations between negative affect and pain measures

As can be observed in Table 3, all correlations between SF-36 Mental health score and pain measures were statistically significant, ranging from -.380 (with the Strongest intensity) to .506 (with Bodily pain at T1). These indicated that less negative affect was related to less pain intensity and less functional interference due to pain.

Preliminary analyses: zero-order and partial correlations between TAS-20 and pain measures

Regarding the zero-order correlations, Bodily pain at T1 correlated significantly with all the TAS-20 subscales and total score (see Table 4). Bodily pain at T2 only correlated significantly with the TAS-20 DIF and the total score. All the pain outcomes at T3 were significantly associated with the TAS-20 DIF and the total score, and the TAS-20 DDF only correlated significantly with Bodily pain at T3 and Pain interference. These results indicated that higher alexithymia levels are related to greater pain intensity and more functional interference due to pain.

Table 4. Zero-order and partial correlations between TAS-20 and pain measures.

	Baseline [e]	**Time 2** [f]			**Time 3** [g]		
Zero-order *r* (*p*)	Bodily pain [h]	Bodily pain	Bodily pain	Average intensity [i]	Strongest intensity [i]	Mildest intensity [i]	Pain interference [i]
DIF [a]	-.347 (.000)	-.270 (.000)	-.337 (.000)	.322 (.000)	.315 (.000)	.284 (.000)	.357 (.000)
DDF [b]	-.201 (.003)	-.121 (.088)	-.244 (.000)	.105 (.137)	.132 (.063)	.128 (.069)	.193 (.006)
EOT [c]	-.137 (.048)	-.067 (.343)	-.056 (.428)	.020 (.778)	.066 (.351)	.002 (.979)	.014 (.846)
TAS-20 total [d]	-.308 (.000)	-.213 (.002)	-.291 (.000)	.218 (.002)	.242 (.001)	.199 (.005)	.266 (.000)
	Baseline	**Time 2**			**Time 3**		
partial *r* (*p*) [j]	Bodily pain	Bodily pain	Bodily pain	Average intensity	Strongest intensity	Mildest intensity	Pain interference
DIF	-.126 (.070)	-.054 (.449)	-.158 (.026)	.192 (.007)	.176 (.013)	.081 (.259)	.152 (.033)
DDF	.010 (.884)	.100 (.162)	-.087 (.226)	-.060 (.402)	-.023 (.745)	-.060 (.402)	-.016 (.828)
EOT	-.015 (.836)	.090 (.210)	.055 (.443)	-.076 (.289)	-.017 (.814)	-.102 (.152)	-.120 (.092)
TAS-20 total	-.070 (.315)	.048 (.505)	-.096 (.182)	.048 (.506)	.079 (.270)	-.024 (.734)	.024 (.738)

[a] DIF = Toronto Alexithymia Scale Difficulty Identifying Feelings subscale. [b] DDF = Toronto Alexithymia Scale Difficulty Describing Feelings subscale. [c] EOT = Toronto Alexithymia Scale Externally Oriented Thinking subscale. [d] The Toronto Alexithymia Scale total score. [e] n = 211 patients. [f] n = 200 patients. [g] n = 201 patients. [h] This subscale belongs to the SF-36 Health Survey. [i] These measures belong to the Brief Pain Inventory. [j] Partial correlations were computed ruling out sociodemographic and negative affect –SF-36 Mental health score– variables.

When sociodemographic variables and Mental health score were ruled out (i.e., partial correlations), only the TAS-20 DIF correlated significantly with pain measures. In particular, the TAS-20 DIF was significantly associated with all pain variables at T3 except for the Mildest intensity (see Table 4). Again, these results indicated that higher alexithymia levels were related to greater pain intensity and more functional interference due to pain.

Relative weight analyses

The percentage of the criterion variance predicted (R^2) by the group of predictors ranged from 34.3% to 20.1% across all models. In particular, the highest proportion was observed when the TAS-20 DIF subscale was included as a predictor and Bodily pain at T1 was the criterion; the lowest percentage was shown in the model in which the TAS-20 total score was included as one of the predictors and the Average intensity was the outcome.

Mental health was statistically different from the random variable in Bodily pain at the three measurement points, Pain interference, the Average, the Strongest and the Mildest intensity, except for Average intensity when the TAS-20 DIF subscale was entered as a predictor. The relative weights associated with Mental health ranged from 46.2% (95% CI 22.7 – 65.6%) to 84.7% (95% CI 64.2 – 91.6%) of the variance predicted by the entire model (see Table 5). The highest relative weight was observed when the TAS-20 EOT subscale was entered as predictor and Pain interference as criterion variable; and the lowest was shown when the TAS-20 DIF subscale was entered as predictor and the Strongest intensity was the criterion variable. All the standardized regression and structure coefficients of Mental health were statistically significant in all the models both in the SF-36 Bodily pain subscale (positive sign) and in the pain intensity and pain interference measures (negative sign), indicating that better mental health (i.e., less negative affect) was related to less pain intensity and less functional interferences due to pain. Regarding the pairwise comparisons, Mental health was generally statistically different from the remaining predictors, except for age in Bodily pain at T3, the Average and Strongest intensity when the TAS-20 total score was entered as predictor, or for age in Bodily pain at T3 when the TAS-20 DDF subscale was entered as predictor. On the contrary, in the models where the TAS-20 DIF

subscale was considered a predictor, Mental health was statistically different from the remaining predictors, except for age (in Bodily pain at T3, the Average and Strongest intensity) or for the TAS-20 DIF (in Bodily pain at T3, Pain interference, the Average, Strongest and Mildest intensity).

The TAS-20 total score was statistically different from the random variable in predicting Bodily pain at T3. It predicted 15.3% (95% CI 6.3 – 30.7%) of the variance explained by the entire model. Its structure coefficient was statistically significant (negative), but not its beta coefficient (see Table 5), indicating that higher alexithymia scores were related to greater pain 18 months after baseline.

The TAS-20 DIF subscale was statistically different from the random variable in predicting Bodily pain at T3 and Pain interference. This subscale predicted 20.5% (95% CI 8.2 – 37.6%) and 28.6% (95% CI 12.3 – 47.1%), respectively, of the variance explained by the entire model. Moreover, its structure coefficient was statistically significant both in Bodily pain at T3 (negative) and Pain interference (positive), but not its beta coefficient (see Table 5), indicating that greater difficulties in identifying feelings were related to greater pain and functional interferences due to pain after 18 months from baseline. However, the TAS-20 DIF subscale was not statistically different from non-significant predictors such as age (except for Pain interference) and gender (except for Average intensity), but it significantly differed from years of education in Bodily pain at T1 and T3, in Pain interference, Average and in the Strongest intensity.

No sociodemographic variable (age, gender or years of education) was statistically different from the random variable.

Table 5. Relative weights, standardized regression coefficients and structure coefficients of the statistically significant predictors.

Predictor	**Criterion variable**	ε [g] **(95% CI)**	β [h] **(95% CI)**	r_s [i] **(95% CI)**	F [j] **(p), R^2**
Mental health [a, b]	Strongest intensity [e]	46.2% (22.7 – 65.6%)	-.284 (-.436/-.121)	-.845 (-.944/-.634)	10.76 (.000), .232
Mental health [c]	Pain interference [e]	84.7% (64.2 – 91.6%)	-.573 (-.701/-.452)	-.925 (-.974/-.791)	15.88 (.000), .336
TAS-20 DIF [d]	Bodily pain [a] at T3 [f]	20.5% (8.2 – 37.6%)	-.141 (-.322/.040)	-.621 (-.787/-.392)	18.36 (.000), .341
TAS-20 DIF	Pain interference	28.6% (12.3 – 47.1%)	.177 (-.022/.366)	.728 (.501/.870)	17.19 (.000), .333
TAS-20 total score	Bodily pain at T3	15.3% (6.3 – 30.7%)	-.064 (-.255/.134)	-.547 (-.733/-.304)	17.44 (.000), .331

[a] These subscales belong to the SF-36 Health Survey. [b] This predictor achieved the lowest relative weight when the Toronto Alexithymia Scale Difficulty Identifying Feelings subscale was entered as predictor. [c] This predictor achieved the highest relative weight when the Toronto Alexithymia Scale Externally Oriented Thinking subscale was entered as predictor. [d] TAS-20 DIF = Toronto Alexithymia Scale Difficulty Identifying Feelings subscale. [e] These measures belong to the Brief Pain Inventory. [f] T3: the third time point of assessment (18 months from baseline). [g] ε = relative weight. [h] β: standardized regression coefficient. [i] r_s: structure coefficient. [j] F, p and R^2 values refer to the entire model where the indicated predictor achieved the statistical significance.

Discussion

The results of the current study reveal the relevant role of negative affect (SF-36 Mental health) in longitudinally predicting several pain outcomes over a period of 18 months in PwMS. Interestingly, when several predictors were jointly considered, difficulties in identifying feelings (the TAS-20 DIF subscale) significantly predicted greater pain and functional interferences due to pain a year and a half after baseline in PwMS. Moreover, within these two models, Mental health was not statistically different from the TAS-20 DIF subscale, so that a major factor to explain pain, namely anxious-depressive symptomatology, was not proven to be more relevant than an alexithymic dimension in longitudinally predicting pain.

In the current study, these two affective constructs, i.e., alexithymia and negative affect, along with three sociodemographic variables (age, gender and years of education) predicted up to 34.3% of the criterion variance, which are percentages similar to those shown in earlier works addressing similar aims (Huber et al., 2009; Makino et al., 2013). Interestingly, in the only study about the relationship between alexithymia and pain in PwMS (Villani et al., 2011), a model including sociodemographic (age, gender and educational level), disease-related (time since MS diagnosis and EDSS score), and psychological variables (fatigue, state/trait anxiety, depression and alexithymia) and co-morbidity with migraine predicted 44% of the variance of the SF-36 Bodily pain subscale. Therefore, a much broader range of variables, both physical and psychological, only added 10% more of explained variance than the percentage shown in our follow-up study.

This study is pioneering in the pain literature due to several reasons: a) it is the first time this statistical approach, i.e., relative weights, is carried out in order to study the relative importance of two affective variables on pain outcomes; b) all the statistical analyses were corrected in terms of measurement error; and c) the relationship between alexithymia and pain has never been addressed through a longitudinal study design in PwMS. Thus, all these facts hinder the comparison of results with previous works.

When alexithymia and negative affect have been jointly addressed with regard to pain outcomes in earlier studies, the statistical approach carried out was based on correlation

analysis (including linear regression models) in clinical populations such as patients with muscular dystrophy (Hosoi et al., 2010), temporomandibular disorder (Glaros & Lumley, 2005), fibromyalgia syndrome (Huber et al., 2009) and outpatients with several pain conditions (Makino et al., 2013; Saariaho et al., 2013). The results derived from zero-order correlations in those works converge with the ones observed in the current study, in the sense of consistent associations between the TAS-20 DIF and the TAS-20 total score with pain interference across studies (Hosoi et al., 2010; Makino et al., 2013; Saariaho et al., 2013). Unlike a previous study (Hosoi et al., 2010) where the TAS-20 EOT correlated significantly with pain intensity and pain interference measures, that alexithymic dimension was uniquely related to SF-36 Bodily pain at baseline in the present work. Conversely, the TAS-20 DIF and the TAS-20 total scores correlated significantly with all the pain intensity outcomes in the current study, as was shown in other studies (Glaros & Lumley, 2005; Hosoi et al., 2010).

In contrast, when sociodemographic and affective-state variables were ruled out in the analyses, findings between studies diverge. Specifically, when the same negative-affect measure as used in this study was administered (i.e., SF-36 Mental health), the TAS-20 EOT and the TAS-20 total score still correlated significantly with pain intensity in patients with muscular dystrophy (Hosoi et al., 2010). However, in the current work, the TAS-20 DIF correlated significantly with pain measures, both of intensity and functional interference, after partialing out the sociodemographic variables and Mental health score. Further, when other measures of negative affect were controlled for, the following divergent results were shown: no TAS-20 score turned out to be a statistically significant predictor of pain measures (Huber et al., 2009; Makino et al., 2013; Saariaho et al., 2013), or the TAS-20 total score and the TAS-20 EOT were statistically significant predictors of pain intensity (Glaros & Lumley, 2005), as observed in Hosoi et al. (2010). Further, in the only study addressing the relationship between alexithymia and pain in PwMS, no TAS-20 score was statistically predictive of pain outcomes (Villani et al., 2011).

Notwithstanding the above, a methodological approach based on partial correlations is flawed because it rules out the influence of a factor, i.e., negative affect, which, although independent, is closely related to alexithymic dimensions (Marchesi et al.,

2000). In fact, this great interrelation between negative affect and alexithymia has been revealed in longitudinal studies where alexithymic levels were shown to be likely state dependent on anxious-depressive symptomatology (Marchesi et al., 2008; Marchesi, Fonto, Balista, Cimmino, & Maggini, 2005; Marchesi et al., 2014). Hence, that is why a relative weight analysis was conducted, as it considers correlated factors both orthogonally and jointly (Johnson, 2000). Thereby, our results derived from partial correlations were strengthened, as the TAS-20 DIF subscale turned out to be a statistically significant predictor of pain outcomes at T3 (Bodily pain and Pain interference) when competing with Mental health in the same model. This finding may be explained by the strong association found between the TAS-20 DIF subscale and affective variables such as depression (Saarijärvi, Salminen, & Toikka, 2001), such that there is not even any statistical difference between them in some models, as was observed in the current study. Also, it could be in keeping with studies finding that this alexithymic dimension, compared with the remaining TAS-20 scores, has been the only statistically significant predictor of pain outcomes in previous works assessing other clinical populations (Huber et al., 2009; Porcelli et al., 2007).

This empirical evidence highlights that the search for the unique predictive role of negative affect versus alexithymia is an unrealistic framework that lacks ecological validity, given that these factors are closely interwoven. Hence, the statistical approach carried out in the present study is the most accurate to disentangle the influence of correlated factors on health outcomes. Accordingly, the fact that some studies report full mediation of negative affect measures, such as depression (Saariaho et al., 2013), in the relationship between alexithymia and pain outcomes does not imply that alexithymia is not a noteworthy construct in order to psychotherapeutically treat the pain experience. Simply, these studies may be showing that negative affect is one of the explanatory mechanisms through which alexithymia may be impacting on pain outcomes. In this sense, based on study designs from which causal inferences can be drawn—i.e., research about treatment efficacy—, a work proved the improvement of pain parameters (intensity and interference) when alexithymia was modified through a multicomponent psychological intervention (Tulipani et al., 2010).

However, the underlying mechanisms that explain the association between alexithymia and greater pain are not yet well understood. A potential hypothesis may take into account the role of somatosensory amplification, as this is positively related to the alexithymia construct (Nakao & Barsky, 2007; Nakao, Barsky, Kumano, & Kuboki, 2002). Nevertheless, it has been reported that people who greatly amplify bodily sensations, measured by the Somatosensory Amplification Scale (Barsky, Wyshak, & Klerman, 1990), do not accurately detect non-pathological interceptive stimuli (Mailloux & Brener, 2002). Hence, cognitive biases may lead to score higher in such self-reported questionnaires (Nakao, Barsky, Nishikitani, Yano, & Murata, 2007) and, thereby, the relationship between somatosensory amplification and alexithymia may be delimited at the cognitive level. Consequently, the way in which the under-identification of interceptive stimuli (i.e., the somatosensory amplification bias) is associated with higher alexithymic levels and greater pain is still an empirical issue to be addressed in further studies, as when significant relationships were found, alexithymia has always been related to higher pain intensity (Makino et al., 2013). Perhaps, research should also focus on the potential deficits in bodily awareness underlying alexithymia and not only on mechanisms of somatic hypersensitivity (Moriguchi & Komaki, 2013). In any event, the somatosensory amplification hypothesis would not be sufficient to explain our results, as we did not observe a mere hypersensitivity to bodily sensations (i.e., higher pain intensity), but instead, the findings of the present study show a link between alexithymia and pain-related problems with clinical significance on a daily basis (i.e., functional interference due to pain). In particular, in the current work, no alexithymic dimension predicted any pure measure of pain intensity in the relative importance analysis, as the SF-36 Bodily pain subscale encompasses both parameters of intensity and interference due to pain. In this sense, difficulties in identifying feelings lead to drawbacks beyond the mere experience of pain itself, as this alexithymic facet mainly affected the PwMS' everyday functioning. In agreement with other studies, this could indicate that alexithymia is more closely linked to the unpleasantness component of pain instead of to its sensory facet (i.e., pain intensity) (Huber et al., 2009; Lumley, Smith, & Longo, 2002).

Moreover, the relative importance analysis conducted in the current study yielded another interesting finding. In particular, alexithymia only predicted pain outcomes in

the longer term. Thus, once the effects of age were statistically taken into account in the model, the TAS-20 total score and the TAS-20 DIF only predicted pain outcomes at T3. Arguably, alexithymia needs time to exert its impact on somatic functioning (Kojima, 2012), as the same subscale (SF-36 Bodily pain) was predicted at T3 but not one year before (T2) or at study entry.

Nevertheless, our findings should be considered taking into account the following limitations. First, even though the study design of the current work, i.e., longitudinal, allows for inferences about temporal precedence, more experimental works are required in order to draw causal explanations. Second, only self-report measures were administered. Nevertheless, several sources of common method bias were avoided in the current study such that the predictors and criterion variables were measured at different points in time, as all predictors were gauged at T1; the various questionnaires presented different scale anchors; and a measure of affective state was statistically taken into account as predictor in all the models (Podsakoff, MacKenzie, Lee, & Podsakoff, 2003). Moreover, the current study addressed the measurement error of the predictors, yielding disattenuated relative weights by using the reliability estimates of the observed measures (Johnson, 2004).

Finally, with the most robust statistical methodology implemented to date and once the temporal precedence in the relationship between various affective measures and pain outcomes has been shown, several clinical implications can be drawn from the current study. First, subgroups at risk of chronic pain within the MS population can be identified. Second, more integrative and multidisciplinary interventions of pain management are needed in order to address the pain experience among PwMS. Third, the psychological component of those treatments should encompass not only anxious-depressive symptomatology, as difficulty to identify feelings has also been shown to be similarly predictive of greater pain and functional interference due to pain 18 months after baseline. Four, learning to differentiate between subjective feelings and somatic sensations related to affective arousal would prevent patients from abusive self-medication with painkillers, so that they would suffer less iatrogenic side effects and their physiological tolerance would decrease, thereby allowing these drugs to be effective when they were really needed.

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5. GLOBAL SUMMARY OF RESULTS

The results will be described according to the two general objectives of the present Ph.D. dissertation:

1) *to determine the relative impact of multiple sclerosis and organ transplantation on patients' quality of life.*

When various dimensions of quality of life (measured by the SF-36 Health Survey) were compared between patients with multiple sclerosis and organ transplant recipients, the results differed as a function of the transplant recipient population to be considered (hepatic or renal), even though worse levels of quality of life were displayed by the neurological patients in all the cases. More specifically, statistically significant differences were observed among the patients with multiple sclerosis compared with liver transplant recipients regarding Role-physical (p = .038) and General health (p = .003), with medium effect sizes. On the contrary, following a longitudinal design, statistically significant differences were found between the neurological patients and renal transplant recipients in Bodily pain (p = .001), Social functioning (p = .004), and Mental health (p = .001), in which worse levels were displayed by patients with multiple sclerosis in both phases. Only Vitality and Physical functioning were statistically different between the neurological patients and both transplant recipient groups in the two works. Further, this latter physical dimension led to an interactive effect, although smaller than the above-mentioned main effect regarding groups, such that patients with multiple sclerosis and renal transplant recipients declined and improved in Physical functioning, respectively, after 6 months from baseline.

Moreover, in both studies, patients with multiple sclerosis showed clinically significant impairment in all the domains of quality of life when their levels were compared with those from the general Spanish population. Similarly, liver transplant recipients showed clinically significant impairment in all the biopsychosocial dimensions, excepting in Mental health; whereas renal transplant recipients only differed from normative values in terms of general health status and daily activity limitations due to physical and emotional problems.

2) *to identify factors predicting a quality-of-life domain, i.e., pain, in patients with multiple sclerosis.*

First, before determining the predictive value of the various dimensions of alexithymia on health parameters, the factorial validity and reliability of an improved Spanish adaptation of the 20-item Toronto Alexithymia Scale (the TAS-20-S) were assessed in a sample of patients with multiple sclerosis. Out of the six different factor models compared, the correlated three-factor model and the higher-order factor model made up of Difficulty Identifying Feelings (DIF), Difficulty Describing Feelings (DDF), and Externally Oriented Thinking (EOT) achieved the best fit, both models showing comparable results. Overall, the standardized factor loadings from these three-factor models were higher in the current study in comparison to those from the previous Spanish version of the TAS-20. The estimates of internal consistency reliability were good for the TAS-20-S total score (.86) and for the DIF subscale (.87), as well as acceptable for the DDF factor scale (.72). Even though the alpha coefficient for the EOT factor scale was questionable (.67), the total scale and the DIF, DDF and EOT factor scales were within the optimal-acceptable range of .20 to .50 for the mean inter-item correlations.

Once the psychometric properties of the TAS-20-S have been proven, this questionnaire can be used in other applied works. In particular, an 18-month follow-up study was conducted in order to analyze the relative importance of alexithymia (measured by the TAS-20-S) and negative affect (measured by the SF-36 Mental health subscale) on the following pain outcomes: SF-36 Bodily pain subscale, pain intensity – average, strongest and mildest ones– and pain interference, in patients with multiple sclerosis. Furthermore, relevant sociodemographic variables and measurement error were taken into account in each statistical model. Negative affect was consistently predictive of pain outcomes, excepting of Average intensity when the TAS-20 DIF subscale was entered as a predictor. All the standardized regression and structure coefficients of Mental health were statistically significant in all the models both in the SF-36 Bodily pain subscale (positive sign) and in the pain intensity and pain interference measures (negative sign), indicating that better mental health (i.e., less

negative affect) was related to less pain intensity and less functional interferences due to pain.

The TAS-20 total score was a statistically significant predictor of Bodily pain after 18 months from baseline (T3). Its structure coefficient was statistically significant (negative), but not its beta coefficient, indicating that higher alexithymia scores were related to greater pain 18 months after baseline.

The TAS-20 DIF subscale was a statistically significant predictor of Bodily pain at T3 and Pain interference and this was not statistically different from Mental health in both models according to pairwise comparisons. Moreover, its structure coefficient was statistically significant both in Bodily pain at T3 (negative) and Pain interference (positive) but not its beta coefficient, indicating that greater difficulties in identifying feelings were related to greater pain and functional interferences due to pain after 18 months from baseline.

No sociodemographic variable (age, gender or years of education) was statistically significant in any model.

6. DISCUSIÓN

A continuación, se discutirán los resultados de cada uno de los cuatro trabajos que conforman la presente Tesis Doctoral; así como, se entrelazarán y analizarán conjuntamente los hallazgos e implicaciones derivadas de varios de estos estudios, cuando proceda.

6.1. Primer y segundo trabajos: estudios comparativos entre pacientes diagnosticados de esclerosis múltiple y trasplantados (hepáticos y renales)

Los resultados de ambos estudios muestran dos perfiles de diferencias biopsicosociales entre pacientes diagnosticados de esclerosis múltiple y trasplantados, en función del grupo de trasplantados al que se apele, esto es, hepáticos o renales; así como distintos niveles de afectación clínicamente significativa según el grupo clínico concreto. En todos los casos, los pacientes neurológicos mostraron peor calidad de vida en aquellos dominios donde se observaron diferencias estadísticamente significativas entre condiciones médicas. Dado que nunca antes se había llevado a cabo la comparación entre estos grupos de pacientes inmunocomprometidos, la explicación de los resultados obtenidos, haciendo referencia a estudios previos en la literatura científica, requiere especial cautela.

En primer lugar, especial énfasis va a ponerse en contrastar la salud mental entre ambas poblaciones clínicas. Este análisis comparativo es la estrategia seguida en la literatura científica sobre esclerosis múltiple (Dalton & Heinrichs, 2005; Drulovic et al., 2007; Holden & Isaac, 2011), con objeto de discernir si la frecuente sintomatología afectiva presente entre estos pacientes es una reacción psicológica ante las limitaciones funcionales y socioeconómicas que genera esta condición neurodegenerativa o, si por el contrario, son síntomas derivados del propio proceso patofisiológico (Sá, 2008). En esta línea, las diferencias entre ambos grupos de trasplantados y los pacientes neurológicos fueron poco relevantes (tamaños de efecto nulos y pequeños) en casi todas las subescalas afectivas del Cuestionario de Salud SF-36 (Salud mental y Rol emocional) (Alonso et al., 1995), a excepción de Salud mental entre pacientes diagnosticados de esclerosis múltiple y trasplantados renales. En concreto, los pacientes neurológicos

mostraron mucha mayor (tamaños de efecto medianos y grandes) sintomatología ansioso-depresiva que los trasplantados renales en ambas fases del estudio.

Las discrepancias en salud mental entre ambos trabajos comparativos podrían ser atribuidas a las características propias del diseño del estudio, de forma que en el primer trabajo, el tiempo transcurrido desde el trasplante hepático hasta la evaluación fue heterogéneo entre los participantes y, por consiguiente, controlado estadísticamente como covariable. En cambio, en el segundo estudio, el tiempo transcurrido desde el trasplante renal hasta la evaluación fue fijo para todos los participantes (transcurridos seis y doce meses, desde la intervención quirúrgica hasta la evaluación biopsicosocial, con respecto a cada una de las fases del estudio, respectivamente). Consecuentemente, las amplias diferencias observadas en salud mental a favor de los trasplantados renales, en comparación con los pacientes neurológicos, podrían explicarse por el alivio y tranquilidad que induce el haberse sometido, recientemente, al tratamiento de elección para combatir su enfermedad renal, tras haber sufrido altos niveles de incertidumbre y anticipación ansiosa durante la fase de lista de espera previa a la intervención del trasplante. No obstante, transcurrido más de un año desde el implante del riñón, estos niveles de bienestar afectivo, medidos por la subescala de Salud mental del Cuestionario de Salud SF-36, podrían descender (Overbeck et al., 2005). Así pues, un ajuste de expectativas más realistas acerca de lo que supone la etapa post-trasplante podría ser la clave de este descenso de salud mental entre trasplantados renales, ya que podrían haber realizado un balance más negativo acerca del fastidio cotidiano de tener que adherirse estrictamente a un tratamiento farmacológico de por vida que no está exento de efectos secundarios perturbadores. Además, este choque con la realidad a largo plazo podría cursar con sentimientos de frustración, máxime cuando las expectativas acerca de las ganancias derivadas del trasplante, en términos de calidad de vida, habían estado sobrestimadas (Smith et al., 2008). Esto podría estar explicando el porqué las diferencias en tal subescala entre pacientes diagnosticados de esclerosis múltiple y trasplantados renales aminoran cuando los pacientes neurológicos son comparados con otras muestras de trasplantados renales (Wei et al., 2013) que se sometieron a la intervención hace más de diez años como promedio (nueve años, como media, transcurrieron desde el diagnóstico de esclerosis múltiple en nuestro segundo trabajo). En esta misma línea, nuestro equipo de investigación llevó a cabo dos estudios que

apoyan aún más esta hipótesis de ausencia de diferencias relevantes en salud mental, entre estas tres condiciones médicas. En primer lugar, demostramos que los niveles de sintomatología ansioso-depresiva fluctúan a lo largo del proceso de trasplante, de manera que las diferencias en salud mental entre trasplantados que han recibido distintos órganos (renal versus hepático) se desdibujan con el transcurso del tiempo (Pérez-San-Gregorio, Fernández-Jiménez, Martín-Rodríguez, Pérez-Bernal, & Gómez Bravo, 2013). Por otro lado, cuando la sintomatología ansioso-depresiva, medida a través de la Escala Hospitalaria de Ansiedad y Depresión (Zigmond & Snaith, 1983), se comparó entre trasplantados hepáticos y pacientes diagnosticados con esclerosis múltiple, no hallamos diferencias relevantes entre grupos después de haber controlado, como covariable, el tiempo desde el diagnóstico de la esclerosis múltiple o el tiempo transcurrido desde el trasplante (Fernández-Jiménez et al., 2011).

Por todo ello, los resultados acumulados, hasta la fecha, por nuestro equipo de trabajo no confirman la hipótesis de que el deterioro afectivo de estos pacientes neurológicos sea meramente atribuible a su condición neurodegenerativa y, por ende, que los pacientes diagnosticados de esclerosis múltiple estén caracterizados por mayores tasas de psicopatología afectiva. En este sentido, hallazgos meta-analíticos (Dalton & Heinrichs, 2005) indican que hay condiciones clínicas en las que la frecuencia/intensidad de la sintomatología depresiva es mayor (p.e., en el Síndrome de Fatiga Crónica) o equiparable (Drulovic et al., 2007) a la observada en pacientes con esclerosis múltiple.

No obstante, estos resultados no son concluyentes, puesto que, si bien los niveles de sintomatología ansioso-depresiva entre estos pacientes neurológicos y otras condiciones médicas no son estadísticamente dispares; cuando se apela a la significación clínica de los resultados en el dominio afectivo, los hallazgos muestran un perfil diferencial entre grupos clínicos. Así pues, con respecto a nuestros dos estudios comparativos, mientras que tanto en trasplantados (hepáticos y renales) y en pacientes diagnosticados de esclerosis múltiple se observa una afectación clínicamente significativa en las actividades cotidianas debido a problemas emocionales (subescala SF-36 Rol emocional); cuando se trata de la frecuencia de sintomatología ansioso-depresiva (subescala SF-36 Salud mental), ambos grupos de trasplantados muestran niveles

equiparables a los de población general frente a la igualmente clínicamente significativa afectación por parte de los pacientes neurológicos en dicha subescala.

Así pues, el debate entre la naturaleza endógena o reactiva del deterioro afectivo, sobre todo, del que concierne al espectro depresivo, no puede plantearse en términos mutuamente excluyentes (Holden & Isaac, 2011). De ahí, que los pacientes con esclerosis múltiple podrían presentar más sintomatología ansioso-depresiva que otros grupos clínicos (p.e., con respecto a otras condiciones neurológicas tales como enfermedades neuromusculares o lesiones medulares) (Dalton & Heinrichs, 2005), máxime si las regiones cerebrales afectadas por la enfermedad median en el procesamiento afectivo; pero esta asociación no es unívoca. Por consiguiente, nuevos enfoques de investigación se requieren para esclarecer este interrogante científico, puesto que aún más variables extrañas deberían ser controladas de cara a comparar condiciones clínicas distintas (Holden & Isaac, 2011).

Por otra parte, las ya mencionadas diferencias en cuanto al diseño de ambos estudios comparativos podrían también explicar por qué los trasplantados hepáticos mostraron deterioro clínicamente significativo en las restantes dimensiones de calidad de vida, a excepción de Salud mental, mientras que los trasplantados renales sólo se vieron clínicamente afectados en términos de salud general y de limitaciones funcionales debido a problemas emocionales o físicos (las subescalas de Rol emocional y Rol físico, respectivamente), transcurridos doce meses del trasplante. Así pues, un seguimiento más extenso de las personas que han recibido un trasplante renal podría haber demostrado un deterioro biopsicosocial más amplio con respecto a los niveles normativos, tal y como han puesto de manifiesto otros estudios sobre la calidad de vida a largo plazo tanto de trasplantados renales (Aasebø, Homb-Vesteraas, Hartmann, & Stavem, 2009; Wei et al., 2013), como de trasplantados hepáticos (Aadahl et al., 2002; Saab et al., 2007), incluso transcurridos más de quince (Kousoulas et al., 2008) y veinte años desde la intervención del implante de hígado (Duffy et al., 2010). Por tanto, se pone de manifiesto la disonancia entre la pronta aceptación fisiológica del injerto frente la ardua integración psicosocial de lo que supone ser una persona que ha sido trasplantada (De Bona et al., 2000); confluyendo en tal adaptación factores de distinta naturaleza que afectan diferencialmente a cada individuo como son las posibles

complicaciones médicas post-trasplante, los efectos secundarios farmacológicos, las dificultades económicas derivadas de los cambios en el status laboral, los niveles de apoyo social, etc.; entre los cuales, el tiempo transcurrido es una variable que posibilita poner en perspectiva el cambio de un status pobre de salud (fases pre-trasplante) por otro no menos exento de adversidades (fase post-trasplante). En la misma línea, otros trabajos también indicaron afectación clínicamente significativa en el funcionamiento biopsicosocial de trasplantados renales y hepáticos, si bien, en un número menor de dominios de calidad de vida con respecto a los valores normativos, ya fuese en estudios realizados en España (Rebollo et al., 2001), Francia (Gentile et al., 2010), Italia (Masala et al., 2012) o China (Wang et al., 2012). No obstante, ninguno de estos trabajos anteriores ajustó estadísticamente las puntuaciones de calidad de vida en función del tiempo transcurrido desde el trasplante, comparándolos con los niveles normativos; de ahí que la comparación con nuestros resultados resulte igualmente difícil. En definitiva, se pone de manifiesto que el trasplante es una intervención que mejora indudablemente los niveles de calidad de vida de personas con hepatopatía o nefropatía terminales, en comparación con las fases pre-trasplante (Martín-Rodríguez et al., 2014; Pérez-San-Gregorio, Martín-Rodríguez, Díaz-Domínguez, & Pérez-Bernal, 2007). Sin embargo, como ya hemos demostrado en un anterior trabajo, la trayectoria de los trasplantados puede ser muy heterogénea (Pérez-San-Gregorio, Martín-Rodríguez, et al., 2013), de manera que algunos pacientes alcanzan niveles equiparables a los normativos, si bien otros sólo se aproximan y/o siguen mostrando deterioro clínicamente relevante tras el trasplante.

Por otro lado, el deterioro biopsicosocial en pacientes con esclerosis múltiple fue clínicamente significativo en todas las dimensiones del Cuestionario de Salud SF-36 en ambos trabajos comparativos. En concreto, las diferencias en los niveles de calidad de vida fueron de magnitud moderada-elevada (tamaños de efecto medianos y grandes), con respecto a los valores normativos provenientes de una muestra representativa de la población general española con edad afín. Estos resultados son particularmente llamativos cuando las dos muestras de pacientes neurológicos fueron evaluadas durante una fase de remisión de, al menos, dos meses de duración. En la misma línea, estos niveles de afectación fueron igualmente observados en el segundo estudio comparativo (diseño longitudinal), cuando las formas progresivas de la enfermedad (primaria y

secundaria) fueron excluidas y los participantes presentaban niveles leves-moderados de discapacidad medidos por la Escala Expandida del Estado de Discapacidad (EDSS) (Kurtzke, 1983).

Además, aunque en el intervalo temporal de seis meses, tanto los pacientes con esclerosis múltiple como los trasplantados renales mantuvieron niveles de calidad de vida similares, a nivel intragrupal, entre ambas fases; un efecto interactivo estadísticamente significativo fue observado en la subescala SF-36 de Funcionamiento físico entre los factores *grupo de pacientes* y *fase del estudio*. En concreto, los pacientes neurológicos mostraron un empeoramiento en el rendimiento de las actividades básicas e instrumentales de la vida diaria, mientras que los trasplantados renales mejoraron en esta dimensión pasados seis meses desde la línea base del estudio. Aunque el efecto principal concerniente al *grupo de pacientes* fue mayor que tal efecto interactivo y los efectos simples referentes a la evolución temporal en cada condición clínica alcanzaron tamaños de efecto pequeños; estas tendencias, si bien estadísticamente significativas, podrían confirmarse con mayor magnitud y hacerse así más patentes si ambos grupos de pacientes fueran seguidos longitudinalmente a lo largo de un período de seguimiento más extenso.

Este deterioro clínicamente significativo en pacientes con esclerosis múltiple ha sido ya observado en numerosos estudios, los cuales también administraron el Cuestionario de Salud SF-36 en muestras de esta población neurológica en países tales como Noruega (Grytten et al., 2012), Alemania (Michalski et al., 2010), Irán (Pakpour et al., 2009), Italia (Casetta et al., 2009; Solari & Radice, 2001), Kuwait (Alshubaili, Ohaeri, Awadalla, & Mabrouk, 2008), Estados Unidos (Pittock et al., 2004), entre otros. No obstante, entre estos trabajos, no se encontró una afectación clínicamente relevante en todas las dimensiones, lo cual resultó más consistentemente con respecto a Rol emocional (Grytten et al., 2012; Michalski et al., 2010; Pittock et al., 2004), Salud mental (Casetta et al., 2009; Michalski et al., 2010; Pittock et al., 2004) y Dolor corporal (Alshubaili et al., 2008; Casetta et al., 2009; Michalski et al., 2010; Pittock et al., 2004; Solari & Radice, 2001); así como, en menor medida, en Funcionamiento social (Alshubaili et al., 2008; Pittock et al., 2004) y Funcionamiento físico (Alshubaili et al., 2008). Estos trabajos ponen así de manifiesto la pertinencia de evitar la estrategia

comparativa que se limita a contrastar los niveles de calidad de vida de una condición clínica con los valores normativos. En este sentido, que en tales estudios la inexistencia de diferencias relevantes, con respecto a los valores normativos, recayese en facetas afectivas de calidad de vida apoyaría nuestra hipótesis del cambio de marco de referencia en personas que han sido diagnosticadas con una enfermedad discapacitante como es la esclerosis múltiple (Oort et al., 2009). Asimismo, la ausencia de deterioro clínicamente significativo en estas dimensiones afectivas en varios de estos estudios cuestiona la naturaleza endógena de la etiología de tal deterioro, ya que incluso cuando se emplearon subescalas específicas para evaluar selectivamente la sintomatología del espectro ansioso y depresivo, no se encontraron diferencias clínicamente relevantes en cuanto a la dimensión depresiva de la Escala Hospitalaria de Ansiedad y Depresión, cuando fue contrastada con valores normativos (Michalski et al., 2010).

Además, los contrastes en niveles de calidad de vida observados en todos estos estudios que implican a diversos países podrían apuntar a un patrón diferencial por regiones, en el cual podrían entrar en concierto factores de distinta naturaleza como son las características sociodemográficas y clínicas propias de la muestra participante en la investigación; el panorama socioeconómico del país en un período histórico determinado en el que se lleva a cabo el estudio; las restricciones para el acceso al sistema sanitario que presenta cada país; variables climatológicas propias de la región; las diferencias culturales que modulan la importancia de las redes de apoyo social en una comunidad, así como la importancia de la autonomía individual, etc. (Pakpour et al., 2009; Pluta-Fuerst et al., 2011).

Por último, el impacto que genera la inmunoterapia en el funcionamiento cotidiano de los pacientes a lo largo del tiempo (Kizilisik et al., 2003; Rommer et al., 2014) pone en valor, una vez más, la idoneidad del análisis comparativo entre pacientes diagnosticados de esclerosis múltiple y aquéllos que han sido trasplantados, dado que ambas poblaciones comparten tratamiento afines. Por ende, este marco de comparación se estima más adecuado que otros estudios comparativos anteriores disponibles en la literatura científica, cuyas muestras clínicas participantes presentaban escasa afinidad en términos de tratamiento o de otros estresores. A su vez, dicha comparación también se ha llevado a cabo de forma longitudinal, a fin de examinar la tendencia de los resultados

cuando transcurrieron seis meses, lo cual apenas se había llevado a cabo entre condiciones clínicas distintas.

6.2. Tercer trabajo: estudio psicométrico sobre la estructura factorial de la Escala de Alexitimia de Toronto (TAS-20) en pacientes diagnosticados de esclerosis múltiple

En primer lugar, los resultados de este estudio apoyan una estructura trifactorial de la TAS-20-S en una muestra española de pacientes con esclerosis múltiple. En concreto, se trata del tradicional modelo de tres factores correlacionados (Bagby et al., 1994), así como de un equivalente modelo trifactorial jerárquico con un factor de segundo orden llamado *Alexitimia global*. Así pues, se confirma que *Dificultad en identificar sentimientos* (DIS), *Dificultad en describir sentimientos* (DDS), y *Pensamiento orientado externamente* (POE) son las dimensiones nucleares del constructo, tal y como es medido por la TAS-20 (Taylor, Bagby, & Parker, 2003). Aunque el uso de puntos de corte pre-establecidos para la evaluación de la bondad de ajuste de los modelos factoriales ha sido cuestionado (Marsh, Hau, & Wen, 2004), los valores obtenidos para ambas estructuras trifactoriales han sido adecuados en el presente trabajo. En este sentido, a pesar de haber sobrepasado ligeramente el umbral de ≤ 1 para el índice Weighted Root Mean Square Residual (WRMR) (Yu, 2002), así como de no haber alcanzado los exigentes puntos de corte de $\geq .95$, determinados por Hu y Bentler (1999), para los índices Tucker–Lewis (TLI) y Comparative Fit (CFI); los resultados de este estudio son aceptables, ya que éstos últimos superaron el umbral de $\geq .90$ (Marsh et al., 2004).

En la misma línea, las estimaciones de fiabilidad de consistencia interna para la escala en su totalidad, así como para las subescalas DIS y DDS fueron aceptables y buenas. Aunque el valor de alpha de Cronbach para la subescala POE fue cuestionable (George & Mallery, 2003) en el presente estudio, éste fue superior al observado en muchas otras adaptaciones de la TAS-20 a distintos idiomas (Taylor et al., 2003; Tsaousis et al., 2010; Zhu et al., 2007). Asimismo, todas las puntuaciones de la TAS-20 fueron entre óptimas y aceptables en términos de correlaciones medias inter-ítem (Briggs & Cheek, 1986).

Por otro lado, en el presente trabajo, la TAS-20 mostró una fiabilidad test-retest estadísticamente significativa tanto en la puntuación total (.57) como en las subescalas DIS (.52), DDS (.61) y POE (.56). En esta misma dirección, dos estudios llevados a cabo en muestras de pacientes oncológicos aportaron correlaciones test-retest comprendiendo el mismo lapso temporal entre medidas que nuestro trabajo (seis meses). En concreto, en un grupo de pacientes oncológicos (diferentes tipos de cáncer) que se sometieron a un tratamiento psicológico, se observaron valores similares a los hallados en la presente investigación (Porcelli, Tulipani, Di Micco, Spedicato, & Maiello, 2011). Por otra parte, en pacientes con cáncer de mama fueron observados valores ligeramente superiores a los observados en el presente trabajo, para la puntuación total de la TAS-20 (.66) y las subescalas DIS (.60), DDS (.64) y POE (.66) (Luminet, Rokbani, Ogez, & Jadoulle, 2007).

Si bien este tercer trabajo que conforma la presente Tesis Doctoral no tuvo como objetivo el análisis de la estabilidad absoluta de la alexitimia, estos resultados apoyan la estabilidad relativa de tal constructo medido por la TAS-20-S. Así pues, mientras que otros trabajos muestran que la alexitimia, al menos, tal y como es medida por tal instrumento, muestra cambios intraindividuales con el transcurso temporal (ausencia de *estabilidad absoluta*), la distancia interindividual del constructo se mantiene similar a lo largo del tiempo (evidencia de *estabilidad relativa*), poniéndose así de manifiesto la necesidad de diferenciar estos dos tipos de estabilidad en la evaluación de constructos psicológicos a los que se le presupone estabilidad temporal, como es el caso de la alexitimia (Santor, Bagby, & Joffe, 1997). Esta estabilidad relativa fue observada en muchos otros trabajos, ya fuesen estudios que contaron con muestras clínicas (Saarijarvi, Salminen, & Toikka, 2006), provenientes de la población general (Salminen, Saarijarvi, Toikka, Kauhanen, & Aarela, 2006); o de estudios donde la alexitimia fue evaluada antes y después de una intervención psicológica (Porcelli et al., 2011). Además, el lapso temporal, entre momentos de evaluación, establecido en esta serie de estudios fue muy amplio, oscilando desde meses hasta once años (si bien en este último trabajo se empleó la versión TAS-26), probándose con ello una extensa estabilidad relativa de este constructo afectivo. No obstante, y como sigue debatiéndose en la actualidad, la evidencia de esta estabilidad relativa no apoya necesariamente la idea de la alexitimia como un rasgo de personalidad que predispone al desarrollo de

diferentes trastornos de distintos espectros psicopatológicos. De hecho, estos estudios longitudinales no permiten extraer inferencias acerca de la relación causal entre alexitimia y otros resultados de salud. Asimismo, la estabilidad temporal de este constructo podría estar condicionada por la presencia concurrente de sintomatología ansioso-depresiva residual (Marchesi et al., 2008; Marchesi et al., 2014), así como por otros factores mediadores y moduladores subyacentes (Santor et al., 1997). En este sentido, otras variables vinculadas al curso clínico de la esclerosis múltiple, aparte de una posible mayor labilidad afectiva, tendrían que ser consideradas para dar cuenta de estos resultados test-retest, como podría ser el progresivo deterioro neuropsicológico en esta población neurológica.

Por último, este tercer trabajo arrojó otro dato relevante en torno a la prevalencia de casos alexitímicos. En concreto, acorde a los puntos de corte determinados en Taylor, Bagby y Parker (1997), altos niveles de alexitimia fueron observados en el 18.1% de la muestra, siendo 20.4% el porcentaje de casos con niveles intermedios en dicho constructo. Estas cifras se aproximan a las indicadas en otros trabajos con muestras de pacientes italianos con esclerosis múltiple, donde se observó un 13.8% de casos con elevada alexitimia (Bodini et al., 2008), o de pacientes franceses, donde estos niveles correspondieron con el 23.2% de la muestra participante (Gay et al., 2010). Porcentajes mayores de casos alexitímicos han quedado reflejados en otros estudios sobre esclerosis múltiple usando la TAS-20 (Chahraoui et al., 2008; Prochnow et al., 2011), si bien los puntos de corte para categorizar a los pacientes con altos niveles de alexitimia fueron más bajos que los establecidos en Taylor et al. (1997).

6.3. Cuarto trabajo: estudio longitudinal sobre la importancia relativa de la alexitimia, afecto negativo, variables sociodemográficas en distintos parámetros de dolor en pacientes diagnosticados de esclerosis múltiple

Una vez probada la estructura factorial de las TAS-20-S, el cuarto trabajo que conforma la presente Tesis Doctoral tuvo como objetivo determinar la importancia relativa de cada una de las dimensiones de la alexitimia, evaluadas por dicho instrumento, con respecto a otras variables afectivas (sintomatología ansioso-depresiva) y sociodemográficas en diferentes parámetros de dolor, a saber, su intensidad y la

interferencia que provoca en distintos dominios de funcionamiento cotidiano en pacientes diagnosticados de esclerosis múltiple.

El estudio del dolor en el presente trabajo estuvo justificado por los tres siguientes motivos, ya estuviesen basados en la literatura científica acumulada; en los resultados empíricos realizados en nuestro equipo de investigación sobre la muestra de pacientes que ha participado a lo largo de los cuatro trabajos de investigación aquí presentados; así como debido a las observaciones clínicas durante la evaluación individualizada de los pacientes. En primer lugar, este cuarto estudio se justificó por la elevada frecuencia con la que estos pacientes neurológicos padecen este síntoma tan discapacitante, la cual se estima en un 62.8%, según recientes hallazgos meta-analíticos (Foley et al., 2013). En segundo lugar, por el impacto clínicamente significativo que tiene el dolor en estas muestras de pacientes participantes, donde en los dos primeros trabajos comparativos se evidenció elevadas diferencias con respecto a los valores normativos tanto de forma transversal como longitudinal. Por último, el presente trabajo está motivado por los consistentes comentarios de los pacientes, a lo largo de las sesiones de evaluación, con los que éstos mostraban su incomprensión acerca de cómo algunos profesionales sanitarios les habían explicado que la experiencia del dolor era atribuible a otros factores independientes de su condición neurológica, con expresiones del tipo "la esclerosis múltiple no duele".

Este cuarto estudio ha puesto de manifiesto el patrón diferencial de relaciones entre las distintas subescalas de la TAS-20 y los diferentes parámetros de dolor. En concreto, la asociación entre la dimensión más cognitiva de la TAS-20 (la subescala POE) con medidas de dolor ha sido limitada a la subescala SF-36 de Dolor corporal únicamente en la línea base del estudio, con una magnitud pequeña. Por el contrario, una de las dimensiones afectivas de la TAS-20, esto es, la subescala DIS, ha sido vinculada a todos los parámetros de dolor en todas las fases del estudio (correlación de orden cero), ha continuado siendo estadísticamente significativa a pesar de haber sido neutralizada la influencia de las variables sociodemográficas y del afecto negativo (correlaciones parciales) y ha mostrado un peso predictivo equiparable (no estadísticamente diferente) al que ejerce una medida de afecto negativo en dos parámetros de dolor (Dolor corporal e interferencia funcional del dolor) pasados dieciocho meses de la línea base. Por todo

ello, el estudio psicométrico realizado previamente, a fin de identificar las distintas dimensiones de la TAS-20-S en una muestra de pacientes con esclerosis múltiple (Fernández-Jiménez, Pérez-San-Gregorio, Taylor, et al., 2013), ha quedado ampliamente justificado en términos de utilidad clínica (Lumley et al., 2007), puesto que dichas subescalas han estado selectivamente vinculadas a diferentes dominios en la experiencia del dolor. En esta misma línea, en otros estudios las subescalas DIS y DDS se vincularon a las fluctuaciones en los niveles de otros constructos afectivos, a saber, depresión y ansiedad, pero esto apenas ocurrió con la subescala POE (Luminet et al., 2007). A su vez, se ha observado que las subescalas DIS y DDS tienen mayor afinidad genética que la que comparten con la subescala POE (Picardi et al., 2011).

En este cuarto trabajo, los distintos modelos estadísticos predijeron entre un 20.1 y un 34.3% de la varianza de las distintas medidas de dolor. A fin de eludir valoraciones acerca de la magnitud de estos porcentajes de predicción, siguiendo unos puntos de corte establecidos *a priori* como los propuestos por Cohen (1988, 1992), los cuales han sido tildados de descontextualizados (Baguley, 2009); dichos porcentajes serán comparados con otros trabajos previos que abordaron conjuntamente los constructos de afecto negativo y alexitimia en la predicción de distintos parámetros de dolor. En concreto, en estos otros estudios donde se incluyeron constructos afines a los contemplados en nuestro trabajo, resultaron porcentajes de varianza explicada del 39% en la predicción de la interferencia funcional debida al dolor en pacientes ambulatorios con diferentes condiciones de dolor (Makino et al., 2013); y del 15% y 33% en la predicción de la tolerancia del dolor al frío y de la faceta afectiva del dolor, respectivamente, en pacientes con fibromialgia (Huber et al., 2009). Curiosamente, en el único estudio que abordó la alexitimia en medidas del dolor en pacientes con esclerosis múltiple (Villani et al., 2011), un modelo predictivo que incluyó variables sociodemográficas (edad, género, nivel educativo), variables relacionadas con la enfermedad (tiempo transcurrido desde el diagnóstico de esclerosis múltiple y puntuación en la Escala Expandida del Estado de Discapacidad), variables psicológicas (niveles de fatiga, ansiedad rasgo/estado, sintomatología depresiva y alexitimia), así como la presencia/ausencia de comorbilidad de migraña, predijo un 44% de la varianza de la subescala SF-36 de Dolor corporal. Por consiguiente, modelos más omnicomprensivos que abarcan factores físicos y psicológicos sólo supuso un 10%

adicional de varianza predicha en medidas de dolor en estos pacientes neurológicos, máxime cuando tal estudio fue transversal y nuestro trabajo predijo un 34% de la varianza de dolor cuando hubieron pasado dieciocho meses de la línea base. Así pues, estos porcentajes cuestionan la idea de que son los factores de naturaleza física los que principalmente explican los resultados en diferentes parámetros de dolor.

Los mecanismos que subyacen a la relación entre alexitimia y mayor experiencia de dolor son aún pobremente entendidos. Curiosamente, un concepto relacionado con el de la alexitimia en los procesos de somatización, esto es, la amplificación somatosensorial (Nakao & Barsky, 2007; Nakao, Barsky, Kumano, & Kuboki, 2002), está más vinculado al procesamiento cognitivo de orden superior, que al interoceptivo (Nakao, Barsky, Nishikitani, Yano, & Murata, 2007), de forma que altas puntuaciones en la Escala de Amplificación Somatosensorial (EAS) (Barsky, Wyshak, & Klerman, 1990) se asocia a una menor sensibilidad a estímulos somáticos benignos (Aronson, Barrett, & Quigley, 2001; Mailloux & Brener, 2002). Por consiguiente, la percepción subjetiva de una función somatoestésica amplificada se debería a alteraciones en el nivel de procesamiento cognitivo, y es ahí donde podría residir el posible punto de conexión con las dificultades alexitímicas. En esta misma línea, otro punto de conexión que poseen ambos constructos reside en su estrecha vinculación con los sentimientos de valencia negativa, hasta el punto que hay autores que han atribuido a las TAS-20 y a la EAS la evaluación de afectividad negativa más que la medición de los constructos que originalmente pretendían captar cuando fueron desarrollados (Aronson et al., 2001; Marchesi et al., in press).

No obstante, la hipótesis de la amplificación somatosensorial no es completamente satisfactoria para dar cuenta de nuestros hallazgos, puesto que ninguna subescala específica de intensidad del dolor fue estadísticamente predicha por ninguna dimensión de la TAS-20 en el análisis de los pesos relativos en nuestro estudio. Por el contrario, nuestros resultados van más allá de una mera asociación entre hipersensibilidad sensorial (esto es, mayor intensidad de dolor) y alexitimia, de forma que las dificultades alexitímicas en la identificación de sentimientos se vincularon a una afectación funcional en la esfera cotidiana debida al dolor (dimensión de interferencia del dolor).

Por otra parte, otro constructo que podría esclarecer la relación entre alexitimia y mayor impacto funcional del dolor podría ser la noción de evitación experiencial. En este sentido, las dificultades alexitímicas podrían también ser conceptualizadas como medios con los que evitar la exposición a eventos privados de naturaleza afectiva. Así pues, en este contexto se fundamenta por qué las intervenciones terapéuticas que abordan la evitación experiencial y promueven la aceptación del dolor y sus consecuencias resultan en beneficios funcionales en pacientes con dolor crónico. En este sentido, el nivel de aceptación hacia la experiencia de dolor se ha relacionado con medidas de actividad funcional y no con la intensidad del dolor (Esteve, Ramírez-Maestre, & López-Martínez, 2007).

Por último, desde un punto de vista psicofisiológico, varios estudios han mostrado un patrón de respuesta diferencial, en función de la tarea experimental concreta, en la corteza cingulada anterior –CCA– en personas con altos niveles de alexitimia (Kano & Fukudo, 2013), siendo ésta una de las regiones cerebrales encargadas de procesar el componente afectivo primario del dolor (Price, 2000). Futuras investigaciones tendrían que ahondar en la relación entre alexitimia y dolor teniendo en cuenta el sistema opioide de analgesia endógeno, el cual está vinculado a la corteza cingulada anterior dorsal, en su parte rostral –CCAr– (Petrovic, Kalso, Petersson, & Ingvar, 2002); ya que las dificultades en el procesamiento afectivo que supone la alexitimia podrían estar interfiriendo en este sistema natural de regulación del dolor (Vallejo-Pareja, 2000). Además, acorde a los hallazgos obtenidos en el presente cuarto trabajo, donde se pone de manifiesto la asociación entre las dificultades alexitímicas y la interferencia del dolor en la esfera funcional, de especial interés clínico podría ser discernir el componente afectivo *primario* versus *secundario* del dolor, ya que este último es el asociado con las repercusiones que puede tener el dolor en la actividad diaria del individuo (Price, 2000).

6.4. Limitaciones y procedimientos de minimización de las mismas en los cuatro trabajos

A continuación se enumeran las posibles limitaciones que han podido presentar estos cuatro trabajos.

En primer lugar, el modesto número de participantes de los dos primeros estudios comparativos compromete la representatividad de las muestras y, por consiguiente, la generalización de los hallazgos. No obstante, dicho tamaño muestral también obedeció a los exigentes criterios de exclusión/inclusión que se impusieron en sendos trabajos. Así pues, para el primer estudio transversal, todos los pacientes con esclerosis múltiple estuvieron sometidos al mismo principio activo como terapia modificadora de la enfermedad (Natalizumab). En este estudio se quisieron descartar otros tratamientos inmunomoduladores, a fin de llevar a cabo un análisis comparativo basado específicamente en inmunosupresores, al ser la modalidad terapéutica empleada entre los trasplantados. Por consiguiente, los principios activos empleados en ambas condiciones médicas podrían exponer a los pacientes a las mismas complicaciones médicas severas (p.e., la leucoencefalopatía multifocal progresiva) (Mateen et al., 2011) y, por tanto, condicionan repercusiones psicológicas similares, entre ambos grupos, en términos de expectativas ansiosas con respecto al pronóstico de su salud. Con respecto al segundo trabajo, el tamaño muestral se vio limitado por el diseño longitudinal del estudio, de manera que fueron seleccionados todos los trasplantados renales posibles, que fueron evaluados transcurridos doce meses de la intervención de trasplante, a fin de ser emparejados con los pacientes diagnosticados de esclerosis múltiple en función de varias variables sociodemográficas.

A su vez, cabría aquí enfatizar que todas las muestras que participaron en los cuatro trabajos que conforman la presente Tesis Doctoral fueron de difícil acceso; ya fuese en cuanto a la disponibilidad de nuevos participantes, en el caso del trasplante de órganos; como en términos de inversión temporal, en el caso de la esclerosis múltiple, dado el elevado tamaño muestral. Con respecto a los participantes de los dos primeros trabajos, todos los trasplantados, hepáticos y renales, provinieron de donantes-cadáver, de forma que no sólo se requirió el fatal desenlace de la persona de la que se extrajeron los órganos, sino que la conformidad con la donación hubo de tramitarse con los familiares del donante en unos momentos de especial sufrimiento, puesto que se trataba de horas posteriores al diagnóstico de muerte, fundamentalmente cerebral, de su ser querido. Asimismo, la también evaluación individualizada de pacientes con una condición neurodegenerativa caracterizada por altos niveles de fatiga física y cognitiva, como es la esclerosis múltiple, hizo de la sesión de evaluación una tarea en la que cuidar todos los

detalles para asegurarse la correcta cumplimentación de la batería de cuestionarios. En este sentido, todos estos pacientes fueron evaluados leyéndoles cada uno de los ítems que conforman las distintas pruebas de evaluación. Consecuentemente, la evaluación de más de doscientos pacientes a lo largo de tres fases de estudio ha supuesto una ingente inversión de tiempo si tenemos en cuenta que se trataba siempre del mismo evaluador.

Con respecto al cuarto trabajo, la sintomatología ansioso-depresiva fue evaluada a través de una subescala del Cuestionario de Salud SF-36 (Salud mental) que engloba ambos espectros psicopatológicos afectivos. Otros instrumentos que presentan dimensiones específicas para cada uno de estos dominios afectivos, como la Escala Hospitalaria de Ansiedad y Depresión –HADS– (Zigmond & Snaith, 1983), fueron descartados al delimitar un marco temporal muy breve, esto es, los últimos siete días, para evaluar esta sintomatología. En este sentido, durante la evaluación de todos los participantes, se ponía de manifiesto cómo según la referencia a una semana u otra la intensidad de la afectación ansioso-depresiva podría ser muy distinta en función de eventos vitales concretos que iban sucediéndose en la vida de los pacientes. Por consiguiente, acorde con trabajos anteriores (Hosoi et al., 2010), se seleccionó la subescala SF-36 de Salud mental para evaluar esta sintomatología ansioso-depresiva durante un marco temporal más extenso (las cuatro últimas semanas), así como para captar, a modo de aproximación, el continuum bipolar afecto negativo-positivo, el cual es más estable en el tiempo. Con ello, frente a estudios recientes que emplearon la escala HADS (Makino et al., 2013), en el presente trabajo se procedió de una forma más próxima a las recomendaciones actuales de incluir constructos de personalidad, afines al afecto negativo y vinculados a la experiencia de dolor, como es el neuroticismo (Ramírez-Maestre & Esteve, 2013).

Asimismo, con respecto a este cuarto trabajo, otra limitación a resaltar radica en la no diferenciación de la muestra entre pacientes que sufren dolor agudo de aquellos que llevan padeciéndolo crónicamente durante más de seis meses. Esto no pudo ser llevado a cabo debido a las dificultades que tuvieron muchos de los participantes en responder a los cuestionarios que apelaban a los siete días previos o a las cuatro semanas anteriores. Así pues, la evaluación con respecto a más de seis meses hubiese estado sesgada y comprometida por estas dificultades mnésicas. No obstante, dicha distinción hubiera

resultado esclarecedora en cuanto a la asociación de variables que nos hemos propuesto estudiar, ya que la literatura vincula las dificultades alexitímicas con el componente afectivo del dolor (Huber et al., 2009; Lumley et al., 2002), y precisamente los pacientes que sufren dolor crónico presentan consistentemente niveles más elevados en tal faceta del dolor, frente aquellos que presentan una condición aguda (Masedo & Esteve, 2002).

Por otra parte, la evaluación de todos los participantes se ha limitado principalmente al uso de cuestionarios, lo cual podría propiciar el sesgo de método común en el cuarto trabajo, al ser el único estudio donde las variables predictoras y criterio provienen de autoinformes. No obstante, en dicho trabajo fueron abordadas diversas fuentes que inducen a dicho sesgo de la siguiente manera (Podsakoff, MacKenzie, Lee, & Podsakoff, 2003): a) mediante la evaluación en distintos momentos temporales de las variables predictoras y criterio, de forma que las primeras fueron todas medidas durante la línea base del estudio; b) a través del uso de diferentes opciones de respuesta en la escala Likert para los distintos cuestionarios [5 opciones categoriales sobre el grado de acuerdo en la Escala de Alexitimia de Toronto (Bagby et al., 1994); 5 opciones categoriales sobre frecuencia en la subescala SF-36 de Salud Mental (Alonso et al., 1995); 6/5 opciones categoriales sobre intensidad/impacto en la subescala SF-36 de Dolor corporal; 11 opciones numéricas en el Cuestionario Breve del Dolor (Badia et al., 2003)]; y c) así como mediante la inclusión de una medida de afecto negativo como una de las variables predictoras a incorporar en todos los modelos, de forma que se tuvo en cuenta estadísticamente la tendencia generalizada a percibirse de forma más desfavorable en términos de salud (en este caso, con respecto al dolor), asociada a elevados niveles de sintomatología ansioso-depresiva.

Además, el uso exclusivo de cuestionarios también tiene otras repercusiones metodológicas y teóricas, en el caso de la evaluación de la alexitimia. En primer lugar, en la literatura científica se ha reclamado evitar la administración exclusiva de autoinformes para medir tal constructo (Taylor & Bagby, 2004), puesto que se pretende evaluar contenidos afectivos en pacientes a los que precisamente se les presuponen marcadas dificultades para introspeccionar su vida emocional, como para poder responder explícitamente a preguntas de tal naturaleza (Moriguchi & Komaki, 2013). En esta dirección, la lectura en voz alta de los diferentes ítems podría haber resultado de

mayor ayuda, tal y como fue llevado a cabo en otros estudios (Pérez-Rincón et al., 1997). A su vez, podría darse la circunstancia de que cuestionarios como la Escala de Alexitimia de Toronto estén únicamente categorizando como alexitímicos a individuos que presentan fundamentalmente déficits cognitivos en el procesamiento emocional; y estén obviándose a personas con limitaciones interoceptivas de base que fenotípicamente presentan dificultades en la consciencia emocional afines a las encontradas bajo la etiqueta de alexitimia. Por consiguiente, hacia las alteraciones alexitímicas se podría confluir a través de la afectación en cualquiera de los dos siguientes niveles implicados en el procesamiento afectivo: el interoceptivo, de orden más primitivo y basal –para cuyo déficit se acuñó la noción de *alexisomia* (Ikemi & Ikemi, 1986)–; y el cognitivo, de orden superior –a cuya afectación propiamente se la ha designado *alexitimia*–. Este modelo jerárquico comprende la participación de diferentes redes neuronales, de manera que el nivel inmediatamente superior modula las fases anteriores del procesamiento emocional, pero no las sustituye. Así pues, toda la literatura que vincula la condición alexitímica con una hipersensibilidad a las respuestas corporales entroncaría con el nivel etiológico de disfunción cognitiva en el procesamiento emocional (Kano & Fukudo, 2013). En cambio, la evidencia empírica que ha asociado altos niveles de alexitimia con una disminuida sensibilidad hacia las sensaciones organísmicas (Herbert, Herbert, & Pollatos, 2011), apoyaría la afectación en el nivel interoceptivo, la cual igualmente conduciría a una ulterior alteración en la consciencia emocional (Moriguchi & Komaki, 2013). Por consiguiente, la amplificación somatosensorial podría encuadrarse al mismo nivel que el de la alexisomia, dado que podría estar vinculada a una alteración en la consciencia interoceptiva, de forma que no se perciban adecuadamente las sensaciones somáticas derivadas de un funcionamiento fisiológico normal.

Por último, de cara a controlar otras posibles fuentes de error en los cuatros trabajos que conforman la presente Tesis Doctoral, a continuación se enumeran otros procedimientos de minimización de los mismos. En los dos primeros estudios comparativos se controlaron estadísticamente variables extrañas por procedimientos de Análisis de la Covarianza (ANCOVA), considerando como covariables la edad y el tiempo desde el diagnóstico de la esclerosis múltiple o el tiempo transcurrido desde el trasplante; así como se efectuó un control en la selección de los participantes a través

del emparejamiento/homogeneización de variables sociodemográficas (género, estatus laboral). Todas estas variables han sido asociadas a resultados de calidad de vida en otros estudios sobre trasplantados renales (Rebollo et al., 2001; Wei et al., 2013), trasplantados hepáticos (Aadahl et al., 2002; De Bona et al., 2000) y pacientes con esclerosis múltiple (Casetta et al., 2009). Asimismo, en el tercer y cuarto trabajo se verificó la inexistencia de un sesgo de participación al no hallarse diferencias estadísticamente significativas en variables sociodemográficas (género, edad) ni relacionadas con la enfermedad (puntuación EDSS o tiempo transcurrido desde el diagnóstico de la esclerosis múltiple) entre los pacientes que finalmente participaron en el estudio frente aquéllos que no. Con respecto al cuarto trabajo, en todo modelo estadístico fue corregido el error de medida teniendo en cuenta los respectivos índices de consistencia interna de cada una de las subescalas implicadas en cada modelo (Johnson, 2004). A su vez, en este estudio no se excluyeron pacientes con ausencia de dolor, como se hizo en otras investigaciones, a fin de no incurrir en problemas derivados de la restricción del rango muestral, los cuales distorsionan la magnitud real de la asociación entre variables (Baguley, 2009).

6.5. Aplicabilidad y utilidad práctica de los resultados en el área de la salud

Los hallazgos derivados de la presente Tesis Doctoral tienen importantes implicaciones tanto sanitarias como a nivel de investigación.

En primer lugar, a nivel *sanitario*, la caracterización de diferentes perfiles biopsicosociales en varias condiciones de salud contribuye al diseño y la implementación de intervenciones diferenciales en función de la población clínica de la que se trate. De esta manera se evitan abordajes asistenciales estandarizados indiscriminados y se maximiza la efectividad de las intervenciones sanitarias en su respectiva población diana. Asimismo, la identificación del impacto relativo que diversas condiciones médicas tienen en la calidad de vida de las personas afectadas por las mismas resulta de gran utilidad de cara a la estimación y asignación diferencial de recursos asistenciales y económicos en el seno de las instituciones hospitalarias (Sprangers et al., 2000; Varni et al., 2007).

Por otro lado, dado el deterioro clínicamente significativo observado entre los trasplantados renales y, sobre todo, hepáticos, en los diversos dominios del funcionamiento biopsicosocial; las intervenciones clínicas a ser implementadas han de ser eminentemente multidisciplinares y comprehensivas (Burra & Germani, 2013). No obstante, una vez establecido el tratamiento médico adecuado para cada receptor, a fin de evitar el rechazo del injerto; las restantes limitaciones biopsicosociales que sufran estas personas debieran abordarse, si fuera posible, desde una perspectiva no farmacológica, con el objetivo de evitar contraindicaciones, interacciones indeseables entre fármacos, así como elevados niveles de toxicidad, dados los complejos regímenes de medicación a los que ya se somete de partida esta población.

Desde la perspectiva de intervención psicológica, el ajuste biopsicosocial que ha de acometerse tras el trasplante expone a esta población a una serie de limitaciones y estresores crónicos que han de inevitablemente integrar en sus vidas, con las repercusiones afectivas que ello conlleva. Por consiguiente, las terapias psicológicas de tercera generación, las cuales fomentan la aceptación del malestar en un proyecto de vida que desarrollar a pesar de tales obstáculos, resultan pertinentes en condiciones médicas crónicas como es el trasplante de órganos.

En este contexto, una técnica como es el mindfulness, la cual es un componente en varias de las terapias psicológicas de tercera generación o en otros programas educativos como es el de Reducción de Estrés mediante Mindfulness (Kabat-Zinn, 1982), podría ser de especial utilidad, tal y como se ha observado en varios estudios empíricos en esta población. En concreto, en un estudio controlado y aleatorio en trasplantados, la aplicación de un programa de Reducción de Estrés mediante Mindfulness redujo los niveles de sintomatología ansiosa, de cansancio, así como los problemas de sueño, y dichas mejoras se mantuvieron a lo largo de un año, en comparación con una intervención control para el automanejo de condiciones médicas crónicas (Gross et al., 2010).

Cabe resaltar aquí la importancia del tratamiento de los problemas afectivos entre trasplantados si atendemos a los resultados derivados de varios estudios. Entre otros hallazgos, la depresión se ha identificado como factor de riesgo de fallecimiento del

receptor o pérdida del injerto a lo largo de un seguimiento de cinco años entre trasplantados renales (Novak et al., 2010; Zalai, Szeifert, & Novak, 2012); así como un mayor nivel de sintomatología ansioso-depresiva, inmediatamente después del trasplante, fue observado en aquellos trasplantados que posteriormente fallecieron a lo largo del primer año tras la intervención quirúrgica (Pérez-San-Gregorio, Martín-Rodríguez, Galán-Rodríguez, & Borda-Mas, 2009).

Por otro lado, desde una perspectiva de intervención fisioterapéutica, el deterioro en dominios físicos de calidad de vida que padecen los trasplantados ha de ser necesariamente abordado, dadas las limitaciones que ello supone en términos de actividades básicas e instrumentales de la vida cotidiana y sus repercusiones, no sólo en el contexto doméstico, sino también en el laboral. En esta misma línea, se ha demostrado que puntuaciones más elevadas en las subescalas SF-36 Funcionamiento físico y Rol físico se han asociado a la reincorporación al mercado laboral tras haber sido trasplantado (Saab et al., 2007), hecho que a su vez, también se ha vinculado a posteriores mejoras en estas dimensiones físicas de calidad de vida cuando tal reincorporación se produjo en los doce primeros meses tras el trasplante (Kousoulas et al., 2008). Asimismo, este tipo de rehabilitación física es crucial, dado que el deterioro en los dominios físicos de calidad de vida predice mortalidad y pérdida del injerto a lo largo de doce años de seguimiento, aun habiendo controlado otros factores de riesgo sociodemográficos y clínicos (Griva, Davenport, & Newman, 2013). Por consiguiente, el valor predictivo de estas facetas físicas de calidad de vida tiene una importancia destacada en esta población de trasplantados, más allá de otros indicadores objetivos de comorbilidad.

Por otra parte, centrándonos en la población de pacientes diagnosticados de esclerosis múltiple, los resultados derivados de los cuatro trabajos que conforman la presente Tesis Doctoral han evidenciado igualmente la necesidad de abordajes omnicomprensivos y multidisciplinares. A continuación, y a colación de los hallazgos obtenidos en los diversos estudios aquí expuestos, profundizaremos en las diferentes intervenciones clínicas que podrían resultar efectivas en esta población neurológica, a fin de abordar los déficits de calidad de vida que presentan, en general, y para prevenir el dolor a largo plazo, en particular.

Así pues, dado que los niveles de deterioro afectivo en esta población neurológica podrían ser estadísticamente equivalentes a los observados en otras condiciones clínicas (en este caso, con respecto a trasplantados) y, por consiguiente, se descarta que la sintomatología ansioso-depresiva se trate de una afectación con etiología meramente neurológica; el tratamiento psicológico en personas con esclerosis múltiple está sobradamente justificado.

Puesto que el papel del estrés percibido en la inducción de actividad inflamatoria de la enfermedad (exacerbaciones y formación de lesiones) entre los pacientes con esclerosis múltiple está aún bajo discusión científica (Heesen & Gold, 2012), investigaciones sobre tratamientos en dicha población clínica que intervengan sobre tal constructo y sus repercusiones podrían resultar prometedoras en el esclarecimiento de algunos aspectos. Para ello, dado su potencial en términos de generalización en el quehacer cotidiano de los pacientes, retomamos aquí la técnica mindfulness, puesto que sus beneficios pueden ser interiorizados y adoptados como estilo de vida a largo plazo. En este sentido, una muy reciente revisión sistemática sobre los escasos estudios que implementaron tal técnica en esclerosis múltiple indicó beneficios en salud mental y calidad de vida, así como el mantenimiento de tales mejoras transcurridos seis meses de la intervención (Simpson et al., 2014). Dado que el deterioro cognitivo es un síntoma muy frecuente en esta enfermedad neurológica, las terapias cognitivo-conductuales estándares, así como los tratamientos basados en mindfulness han sido cuestionados para pacientes con déficits neuropsicológicos (Feinstein, 2011). No obstante, una estrategia para la compensación de tal limitación es la implementación de una serie de adaptaciones en las intervenciones cognitivo-conductuales tradicionales, tales como mayor énfasis en técnicas conductuales, simplificación de las tareas, establecimiento de una alianza terapéutica con algún familiar que colabore en la realización de las tareas que ha de desarrollar el paciente en casa, entre otras (Rabinowitz & Arnett, 2013).

Centrándonos ya en el dolor como objetivo de intervención, la identificación de predictores tratables de naturaleza afectiva en variables de salud tan discapacitantes como es el dolor redundará en un servicio asistencial adecuado, que reducirá los posibles efectos iatrogénicos asociados a tratamientos meramente sintomáticos, a favor

de un abordaje terapéutico más integrador donde el paciente aprenda a minimizar una abusiva automedicación con analgésicos. En este contexto, hemos propuesto la intervención sobre variables como son la sintomatología ansioso-depresiva y las dificultades alexitímicas, dada su vinculación con distintos parámetros de la experiencia de dolor, tanto a nivel sensorial (intensidad del dolor) como a nivel funcional (interferencias en actividades cotidianas debidas al dolor). Especial énfasis hemos puesto en el constructo de la alexitimia, dada la amplia literatura acumulada hasta la fecha que lo vincula con tantas condiciones de salud, entre ellas, el dolor, si bien escasos han sido los estudios longitudinales y de tratamiento que han abordado su contribución en la experiencia de dolor. Así pues, más investigación sobre intervenciones psicológicas que incidan en las dificultades alexitímicas es requerida en pacientes con dolor, máxime cuando estudios recientes advierten de las repercusiones negativas de tal constructo en esta población. Por ejemplo, mayor frecuencia de dolor se ha asociado con mayor dependencia a analgésicos cuando tales personas presentaban niveles elevados de alexitimia, y tal dependencia era menor cuando las dificultades alexitímicas eran leves, aunque la frecuencia de dolor fuera igualmente elevada (Elander, Duarte, Maratos, & Gilbert, 2014).

Esta línea de tratamiento viene apoyada por la evidencia científica acumulada hasta la fecha, la cual apunta que la alexitimia no es meramente un rasgo de personalidad, sino un constructo que podría depender fundamentalmente del estado afectivo concurrente (Marchesi et al., 2008; Marchesi et al., 2005; Marchesi et al., 2014). A su vez, sus factores etiológicos son, en gran medida, de naturaleza ambiental (Picardi et al., 2011), por lo que la posibilidad de que la alexitimia sea modificada a través de intervenciones psicoterapéuticas está asegurada, tal y como han puesto de manifiesto algunos estudios de tratamiento en la población general, así como en muestras clínicas afectadas por trastornos psicopatológicos (Rufer et al., 2010) y por enfermedades médicas (Beresnevaite, 2000; Melin, Thulesius, & Persson, 2010; Tulipani et al., 2010).

Entre los estudios anteriores donde el dolor fue una variable de resultado, un descenso en los niveles del mismo estuvo asociado a una disminución de las dificultades alexitímicas, en una investigación en pacientes con distintos tipos de cáncer (Tulipani et al., 2010); así como una menor frecuencia de dolor pectoral fue observada en pacientes

con patología cardíaca que participaron en el grupo de intervención, frente al grupo control, junto con una disminución de los niveles alexitímicos (Beresnevaite, 2000), si bien en este último trabajo la evaluación del descenso del dolor no fue estandarizada. No obstante, esta asociación no fue observada en otro trabajo, donde se mostró una mejora en la dimensión alexitímica tras la intervención psicológica, pero no en los niveles de dolor (Melin et al., 2010).

Así pues, las posibles discrepancias existentes entre las escasas investigaciones que tratan el dolor interviniendo sobre la alexitimia podrían atribuirse al énfasis diferencial que se podría haber puesto en las distintas dificultades alexitímicas. En este sentido, los hallazgos del cuarto trabajo que conforma esta Tesis Doctoral guían acerca de cuáles serían los contenidos y técnicas específicas que deberían programarse de cara a implementar tratamientos para el manejo del dolor en personas con esclerosis múltiple. En concreto, mayor atención debería ponerse en las dificultades para la identificación de sentimientos/emociones, así como su diferenciación de las sensaciones somáticas vinculadas al aurosal afectivo. Como corolario, de gran utilidad podrían resultar las técnicas que promueven la autorregulación tales como el mindfulness o la hipnosis (Vallejo-Pareja, 2006) entre pacientes diagnosticados de esclerosis múltiple con elevados niveles de alexitimia, dada la tendencia al pensamiento externamente orientado y, por ende, a la evitación de las vivencias subjetivas que implica este constructo afectivo. El fundamento común a estas técnicas radica en permitir a los pacientes experimentar de manera genuina todas las sensaciones somáticas y afectivas que estén sucediéndose, a fin de activar los *servomecanismos* endógenos corporales (Vallejo-Pareja, 2006).

En concreto, la aplicación de intervenciones basadas en mindfulness sólo ha sido abordada a través de tres estudios controlados en pacientes con esclerosis múltiple (Simpson et al., 2014) y el único trabajo que investigó el impacto de dichas técnicas en el dolor (subescala SF-36 de Dolor corporal), aunque mostró una reducción estadísticamente significativa del mismo, estuvo caracterizado por las siguientes limitaciones: un tamaño muestral muy reducido (n = 17: 10 en el grupo de intervención y 7 pacientes asignados al grupo control), ninguna fase de evaluación de seguimiento, una asignación no aleatoria de los participantes, así como otras fuentes de sesgo (Tavee,

Rensel, Planchon, Butler, & Stone, 2011). Curiosamente, en el único estudio controlado que aplicó la técnica mindfulness en la población trasplantada (Gross et al., 2010), ninguna mejoría se obtuvo con respecto al dolor. Por consiguiente, dada la amplia evidencia empírica que avala la efectividad de los programas basados en mindfulness para la reducción de la percepción de dolor, más investigaciones serían necesarias para explicar esta ausencia de respuesta; en las cuales podrían examinarse la sensibilidad al cambio de diferentes aspectos del dolor entre trasplantados, como son su etiología (ya fuese de naturaleza más nociceptiva versus neuropática), así como su componente afectivo frente a su faceta sensorial. A su vez, otro eje de análisis sería la modalidad de mindfulness a entrenar, ya que tanto la modalidad zen como la tibetana disminuyen el componente afectivo del dolor, pero no es así con la dimensión sensorial del mismo si es aplicada la tradición tibetana (Grant, 2014).

Además, un interesante resultado del cuarto trabajo desarrollado en esta Tesis Doctoral es que las dificultades en la identificación de sentimientos predijeron varios parámetros del dolor únicamente a largo plazo (pasados dieciocho meses desde la línea base), pero no de forma concurrente (en la línea base) ni a corto plazo (pasados seis meses) (Kojima, 2012). Por ende, el papel de la alexitimia en el tratamiento del dolor se enmarcaría en los objetivos de prevención más que de paliación del mismo a corto plazo. Aquí volvemos a enfatizar la diferenciación entre el componente afectivo primario y secundario del dolor, éste último más implicado en la anticipación negativa que el dolor podría causar en la esfera funcional del paciente en un futuro (Price, 2000).

Por último, a nivel de *investigación*, la identificación de la estructura factorial de la Escala de Alexitimia de Toronto (TAS-20) en esclerosis múltiple estimulará la implementación de nuevos estudios en dicha población donde se examine el valor predictivo diferencial de cada una de las dimensiones de dicho instrumento con respecto a diferentes parámetros de salud.

Por otra parte, el esclarecimiento del impacto relativo que distintas condiciones médicas tienen sobre la calidad de vida de sus afectados contribuye a la toma de decisiones, por parte de las administraciones públicas y entes privados, sobre la asignación de fondos de financiación para la investigación (Sprangers et al., 2000). En

este sentido, dado el amplio deterioro clínicamente significativo demostrado en la presente Tesis Doctoral, tanto la esclerosis múltiple como el trasplante de órganos deben seguir siendo poblaciones clínicas prioritarias con respecto a la aprobación de proyectos de investigación a ser financiados.

7. CONCLUSIONS

On one note, the present Ph.D. dissertation aimed to analyze the relative impact of multiple sclerosis and organ transplantation on patients' quality of life.

In this sense, the differences between both clinical populations were conditioned by the specific transplant recipient group with which the neurological patients were compared, even though the worst quality-of-life levels were observed among these patients with multiple sclerosis. In particular, the neurological patients were more impaired in physical domains of quality of life when they were compared with liver transplant recipients. Conversely, they were more broadly affected regarding physical and psychosocial dimensions when the comparison was carried out with renal transplant recipients. Tiredness and lack of energy was statistically more marked in patients with multiple sclerosis regardless of the transplant recipient population (hepatic or renal) with which they were compared.

Overall, both renal transplant recipients and patients with multiple sclerosis retained similar levels of biopsychosocial functioning after 6 months from baseline, although renal recipients presented a trend to improvement in basic and instrumental activities of daily living, reaching normative levels at that time; while patients with multiple sclerosis showed a trend to impairment in this physical dimension.

When these three clinical populations under similar pharmacological treatment, i.e., immunotherapy, are contrasted, the severity of the biopsychosocial impairment suffered by the patients with multiple sclerosis is highlighted, be it by being compared with both transplant recipient groups or with the general Spanish population. However, these groups of patients who have undergone their treatment of choice, namely organ transplantation, continue to require specialized health care after the surgical intervention, because they still show relevant difficulties in daily functioning due to their health problems, compared with the general population. Interestingly, they did not show statistically significant differences in several quality-of-life domains in comparison to a population with a neurodegenerative condition.

On another note, the present Ph.D. dissertation aimed to determine the relative importance of affective factors (alexithymia and negative affect) on quality-of-life dimensions, namely pain, but previously, the dimensionality of the instrument to measure alexithymia had to be studied.

In this sense, when the factor validity of an improved Spanish adaptation of the 20-item Toronto Alexithymia Scale (TAS-20-S) was examined in a sample of patients with multiple sclerosis, both a correlated three-factor model and a higher-order factor model achieved the best fit, both showing comparable results. In particular, the former was made up of Difficulty Identifying Feelings (DIF), Difficulty Describing Feelings (DDF), and Externally Oriented Thinking (EOT); and the latter comprised the same three factors and, in turn, these also formed a second-order factor named Global Alexithymia. Therefore, this finding confirms the factor structure shown in the original English version of the TAS-20. Further, the refinement of the Spanish version of the TAS-20 led to the improvement of several psychometric properties (goodness-of-fit indices as well as the factor loadings of the items modified) compared with earlier Spanish versions of the scale.

Moreover, taking together both the alpha coefficients and the mean inter-item correlations for the total scale and its factor scales, the TAS-20-S showed good-acceptable reliability. Hence all three factor scales of the TAS-20-S can be considered homogeneous, and can be scored along with the TAS-20-S total score in studies with populations affected by multiple sclerosis.

Therefore, from these findings, further applied studies can be conducted where the TAS-20 might be used to investigate the clinical relevance and differential predictive value of each of the three facets of the alexithymia construct, measured by such instrument, in people with multiple sclerosis.

Accordingly, an 18-month follow-up study was conducted in order to analyze the relative importance of the various dimensions of alexithymia, measured by the TAS-20-S, on several pain parameters, namely pain intensity and functional interferences due to pain. Further, negative affect and sociodemographic variables were together analyzed in

the same model where the measurement error of the questionnaires was also taken into account. Likewise, the statistical approach carried out in the present study, based on relative weights, is the most accurate to disentangle the influence of correlated factors on health outcomes, since it statistically analyzes them both orthogonally and jointly. Therefore, the search of the unique predictive role of negative affect against alexithymia is an unrealistic framework which lacks ecological validity, given that these factors are closely interwoven.

The results of the current study evidence the relevant role of negative affect (SF-36 Mental health) in longitudinally predicting several pain outcomes over a period of 18 months. Interestingly, when several predictors were jointly considered, difficulties in identifying feelings (the TAS-20 DIF subscale) significantly predicted greater pain and functional interferences due to pain after a year and a half from baseline in patients with multiple sclerosis. Moreover, within these two models, Mental health was not statistically different from the TAS-20 DIF subscale, in such a way that a major factor to explain pain, namely anxious-depressive symptomatology, was not proven to be more relevant than an alexithymic dimension in longitudinally predicting pain in this clinical population.

Once the temporal precedence in the relationship between various affective measures and pain outcomes has been shown, several clinical implications can be drawn from the current study. Among them, these results imply that the psychological treatments addressing pain experience in PwMS should encompass not only anxious-depressive symptomatology, as difficulty in identifying feelings has also been shown to be similarly predictive of greater pain and functional interference due to pain.

8. RESUMEN / SUMMARY

En la presente Tesis Doctoral se han llevado a cabo cuatro trabajos empíricos y pioneros que abordan el funcionamiento biopsicosocial de pacientes diagnosticados de esclerosis múltiple y de trasplantados (hepáticos y renales). El nivel de análisis de este conjunto de investigaciones oscilará desde lo más omnicomprensivo (todas las dimensiones de calidad de vida), en los dos primeros trabajos; hasta dominios concretos del funcionamiento biopsicosocial (dificultades en el procesamiento afectivo y el dolor), en el tercer y cuarto estudios.

En concreto, en los dos primeros trabajos se propuso comparar la calidad de vida de pacientes diagnosticados de esclerosis múltiple y trasplantados (hepáticos y renales) para así determinar el impacto relativo que ambas condiciones médicas ejercen sobre el funcionamiento biopsicosocial de sus afectados. El *Cuestionario de Salud SF-36* fue el instrumento administrado a las siguientes muestras de participantes: a) con respecto al primer trabajo, 31 pacientes con esclerosis múltiple y 31 trasplantados hepáticos, ambos grupos apareados por género; b) referente al segundo estudio, 30 pacientes con esclerosis múltiple y 30 trasplantados renales, ambos grupos apareados por género y homogeneizados en función de la edad y el estatus laboral. El Análisis de la Covarianza fue aplicado en los dos estudios, controlando el tiempo transcurrido desde el diagnóstico de la esclerosis múltiple/tiempo desde la intervención del trasplante (en el primer trabajo), así como controlando la edad (en el segundo estudio) como covariables.

El marco comparativo que conforman ambos trabajos resulta muy acertado desde un punto de vista clínico, puesto que ambas poblaciones comparten la inmunoterapia como tratamiento farmacológico principal, siendo expuestas así a estresores afines. A su vez, estos dos trabajos presentaron diseños de estudio complementarios, transversal (el primero) y longitudinal (el segundo), de manera que incluso se pudo determinar la trayectoria de las diferencias entre grupos a lo largo de seis meses desde la línea base del estudio. Por último, todos estos resultados fueron analizados en términos de significación clínica, utilizando para ello dos muestras representativas de la población general española en función del intervalo de edad pertinente para la muestra participante en cada estudio.

En todos los dominios en los que hubo diferencias estadísticamente significativas entre condiciones clínicas, los pacientes neurológicos mostraron peores niveles de calidad de vida; perteneciendo éstas a la esfera física, cuando el contraste fue llevado a cabo con trasplantados hepáticos; mientras que las diferencias fueron más amplias, tanto a nivel físico, como psicosocial, cuando la comparación implicó a los trasplantados renales. Además, mientras que los pacientes diagnosticados de esclerosis múltiple mostraron un deterioro clínicamente relevante en todas las dimensiones de calidad de vida en ambos trabajos y fases; los trasplantados, sobre todo, los trasplantados hepáticos, mostraron también deterioro clínicamente significativo en varias facetas del funcionamiento biopsicosocial. Por consiguiente, se pone de manifiesto que tanto estos pacientes neurológicos como los trasplantados son poblaciones médicas que requieren especial atención sanitaria.

El tercer trabajo que conforma la presente Tesis Doctoral fue igualmente pionero a nivel científico, al ser la primera vez que se estudiaba la estructura factorial de la *Escala de Alexitimia de Toronto* (TAS-20) en pacientes diagnosticados de esclerosis múltiple; así como al ser el primer trabajo que abordó la alexitimia en estos pacientes neurológicos en España. Asimismo, en este estudio se propuso una versión mejorada de la adaptación en español de dicho instrumento (designada así TAS-20-S), con respecto a las ya disponibles en nuestro idioma. Este trabajo, en el cual participaron 221 pacientes, apoyó la estructura trifactorial tradicional de la TAS-20 a través de un análisis factorial confirmatorio, así como demostró unos niveles adecuados de fiabilidad para la escala en su totalidad y para cada una de sus subescalas. Por tanto, tales hallazgos justifican la realización de futuros trabajos empíricos que evalúen el valor predictivo diferencial de cada una de las dimensiones de la alexitimia tal y como es medida por la TAS-20.

En línea con lo anterior, el cuarto trabajo tuvo como objetivo determinar la importancia relativa de las distintas subescalas de la TAS-20-S con respecto a otras variables de naturaleza afectiva (sintomatología ansioso-depresiva medida a través de la subescala de Salud mental del *Cuestionario de Salud SF-36*) y sociodemográfica (edad, género y nivel educativo); a fin de predecir distintos parámetros del dolor (intensidad e interferencia funcional mediante el *Cuestionario Breve del Dolor*; y la subescala de Dolor corporal del *Cuestionario de Salud SF-36*) en pacientes con esclerosis múltiple.

Siguiendo un diseño longitudinal (línea base –211 pacientes–, transcurridos seis –200 pacientes– y dieciocho meses –201 pacientes–), se empleó un procedimiento estadístico novedoso basado en pesos relativos de cara a efectuar un análisis de la contribución de cada predictor de forma más realista, teniendo en consideración la correlación real existente entre variables y el error de medida de cada predictor. Todos los predictores pertenecieron a la línea base del estudio. La sintomatología ansioso-depresiva predijo significativamente los distintos parámetros del dolor en todos los modelos, a excepción de uno. A su vez, la subescala de la TAS-20-S Dificultad en Identificar Sentimientos predijo de forma estadísticamente significativa la subescala SF-36 Dolor corporal y la interferencia funcional del dolor, ambos parámetros pertenecientes a la tercera fase del estudio, cuando habían transcurrido dieciocho meses de la línea base. Curiosamente, en estos dos últimos modelos donde Dificultad en Identificar Sentimientos fue un predictor estadísticamente significativo, no se encontraron diferencias significativas entre dicha dimensión alexitímica y la sintomatología ansioso-depresiva de cara a predecir tales facetas del dolor (SF-36 Dolor corporal y la interferencia funcional del dolor). Estos resultados indican que las intervenciones psicológicas que traten el dolor en pacientes con esclerosis múltiple deberían abordar tanto el afecto negativo como la dificultad alexitímica de identificar y diferenciar sentimientos de las sensaciones somáticas asociadas al arousal afectivo.

In the present Ph.D. dissertation, four empirical and pioneering works have been carried out addressing the biopsychosocial functioning of patients diagnosed with multiple sclerosis (MS) and of transplant recipients (hepatic and renal). The level of analysis of this group of pieces of research will range from a general level (all quality-of-life dimensions) in the first two papers, to specific domains of the biopsychosocial functioning (difficulties in affective processing and pain) in the third and fourth studies.

Particularly, the first two works aimed to compare the quality of life of patients diagnosed with MS and of transplant recipients (hepatic and renal) in order to determine the relative impact that these medical conditions have on the biopsychosocial functioning of the affected people. The *SF-36 Health Survey* was administered to the

following participant samples: a) with respect to the first work, 31 patients with MS and 31 liver transplant recipients, both groups matched for gender; b) regarding the second study, 30 patients with MS and 30 renal transplant recipients, both groups matched for gender and homogenized according to age and working status. Analysis of Covariance was conducted in both studies, controlling for time since diagnosis of multiple sclerosis/time since transplantation surgery until assessment (first work), and controlling for age (in the second study) as covariates.

The comparative framework underlying both works is very suitable from a clinical point of view, as both populations share immunotherapy as a pharmacologic first-line treatment, thereby being exposed to similar stressors. Likewise, these two studies presented complementary study designs, cross-sectional (the first one) and longitudinal (the second one), so that the trajectory of the differences between groups could even be determined at six months from baseline. Finally, all these results were analyzed in terms of clinical significance, using two representative samples of the general Spanish population according to the specific age interval of the participant sample involved in each study.

In all domains in which statistically significant differences between both clinical conditions were found, neurological patients showed worse quality-of-life levels. These differences belonged to the physical domain when the comparison with liver transplant recipients was carried out, whereas the differences were broader, both in physical and psychosocial facets, when the contrast involved renal transplant recipients. Moreover, while patients diagnosed with multiple sclerosis showed a clinically relevant deterioration in all dimensions of quality of life in both works and measurement points, transplant recipients, and especially liver transplant recipients, also showed clinically significant impairment in several domains of the biopsychosocial functioning. Therefore, it becomes clear that both these neurological patients and transplant recipients are medical populations that require special health care.

The third work included in this Ph.D. dissertation was also pioneering from a scientific standpoint, by being the first work that studied the factor structure of the *Toronto Alexithymia Scale* (TAS-20) in patients diagnosed with multiple sclerosis, as

well as the first work that addressed alexithymia in these neurological patients in Spain. Furthermore, in this study, an improved version of the Spanish adaptation of this instrument was proposed (named the TAS-20-S), with respect to those ones already available in our language. This work, which involved 221 patients, supported the traditional three-factor structure of the TAS-20 using confirmatory factor analysis, and showed appropriate reliability levels for the total scale and for each of its subscales. Therefore, these findings justify conducting future empirical research in order to assess the differential predictive value of each of the dimensions of alexithymia as measured by the TAS-20.

In line with this, the fourth study aimed to determine the relative importance of the various subscales of the TAS-20-S with respect to other variables of an affective (anxious-depressive symptomatology measured by the Mental health subscale of the *SF-36 Health Survey*) and sociodemographic nature (age, gender and educational level), to predict various parameters of pain (intensity and functional interference using the *Brief Pain Inventory*, and the Bodily pain subscale of the *SF-36 Health Survey*) in patients with MS. Using a longitudinal design (baseline –211 patients–, at 6 months –200 patients– and at 18 months –201 patients), a new statistical method based on relative weights was used to perform a more realistic analysis of the contribution of each predictor, taking into account the actual correlation between variables and the measurement error of each predictor. All predictors belonged to the baseline of the study. Anxious-depressive symptomatology significantly predicted the various parameters of pain in all models, except for one. In turn, the subscale of the TAS-20-S, Difficulty Identifying Feelings, statistically predicted the SF-36 Bodily pain subscale and functional interference due to pain, both parameters belonging to the third measurement point of the study –18 months after baseline. Interestingly, in the latter two models where Difficulty Identifying Feelings was a significant predictor, no statistically significant differences were found between this alexithymic dimension and anxious-depressive symptomatology in predicting the above-mentioned facets of pain (SF-36 Bodily pain subscale and functional interference due to pain). These results indicate that psychological interventions to treat pain in patients with MS should address negative affect and alexithymic difficulty identifying feelings as well as

differentiating between feelings and the somatic sensations associated with affective arousal.

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10. ANEXOS

10.1. Separata del artículo titulado "*Comparison of quality of life between two clinical conditions with immunosuppressive therapy: Liver transplantation and multiple sclerosis*"

Comparison of Quality of Life Between Two Clinical Conditions With Immunosuppressive Therapy: Liver Transplantation and Multiple Sclerosis

E. Fernández-Jiménez, M.A. Pérez-San-Gregorio, A. Martín-Rodríguez, E. Domínguez-Cabello, G. Navarro-Mascarell, and A. Bernardos-Rodríguez

ABSTRACT

Objective. We aimed to compare quality of life in two clinical conditions treated with immunosuppressants: cadaveric liver transplant recipients and multiple sclerosis patients. We also assessed the clinical significance of these results regarding a representative age-adjusted sample of the general Spanish population.

Methods. Using a cross-sectional design, the SF-36 Health Survey was used to evaluate 62 patients with these chronic conditions (31 in each group) who were matched for gender. An analysis of covariance was performed to control for the influence of time from multiple sclerosis diagnosis and liver transplantation surgery until assessment. Student t test of covariate-adjusted mean values was used as the statistical test and Cohen's d effect size index, to assess the magnitude of intergroup differences and assess clinical significance.

Results. Significantly worse scores were observed among the neurological patients compared with transplant recipients regarding role-physical ($P = .038$), general health ($P = .003$), vitality ($P = .034$), and physical functioning ($P = .049$), with medium effect sizes (Cohen's ds from -0.511 to -0.785). Against normative values, liver transplant recipients displayed relevant differences in all SF-36 subscales (Cohen's ds from -0.569 to -0.974) except for mental health (small effect size). Likewise, multiple sclerosis patients showed much greater differences versus the general population (Cohen's ds from -0.846 to -1.760).

Conclusions. Liver transplant recipients showed better quality of life than multiple sclerosis patients (medium effect sizes) in physical quality-of-life dimensions. Interestingly, despite having controlled for time from diagnosis/transplantation, both medical conditions showed clinically significant impairments (large and medium effect sizes) in physical and psychosocial quality-of-life domains. We concluded that transplant recipients belong to a population that still requires special health care because, even after having undergone their treatment of choice, they do not achieve normal levels of biopsychosocial functioning.

THE assessment of quality of life (QoL) among liver transplant recipients versus pretransplantation patients or the general population has been widely studied.[1,2] However, the general population does not usually undergo the chronic stressors related to a lethal or disabling disease. Consequently, it is sometimes reported that liver transplant

From the Faculty of Psychology, Department of Personality (E.F.-J., M.A.P.-S.-G., A.M.-R., E.D.-C.), Assessment, and Psychological Treatments, University of Seville, the Multiple Sclerosis Unit (G.N.-M.), University Hospital Virgen Macarena of Seville, and the Hepatic-Biliary-Pancreatic Surgery and Liver Transplant Unit (A.B.-R.), University Hospital Virgen del Rocío of Seville, Seville, Spain.

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Address reprint requests to Mª Ángeles Pérez-San-Gregorio, Facultad de Psicología. Departamento de Personalidad, Evaluación y Tratamiento Psicológicos. C/Camilo José Cela, s/n, 41018, Sevilla, Spain. E-mail: anperez@us.es

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recipients enjoy better QoL than the general population,[3] maybe due to phenomena such as the response-shift, which is explained by patients' frames of reference having changed after the experience of a chronic disabling disease, ie, accepting that full recovery is impossible. This possibility might be observed when they answer questionnaires.[4] One solution for a more relevant comparison would be an evaluation with reference to another chronic disease group with some similarities. In this sense, multiple sclerosis (MS) may be a valid contrast group because both they and liver transplant recipients are immunocompromised, which could induce similar therapy-related complications.[5] Therefore, we sought to compare QoL between liver transplant recipients and MS patients and assess the clinical significance of these results regarding the general Spanish population of similar age.

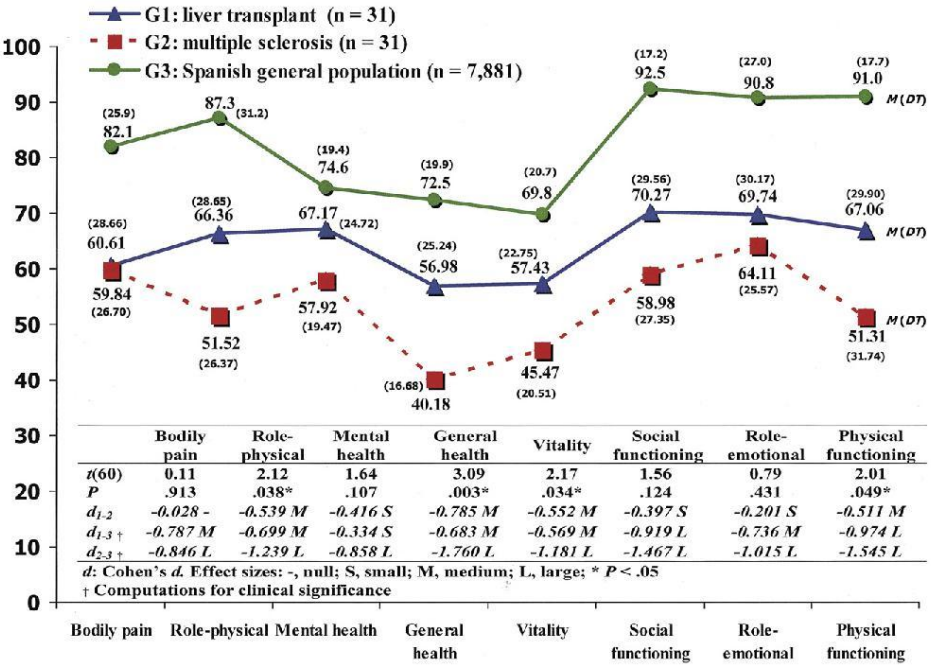
METHODS

Selection and Description of Participants and Statistical Techniques

The participant sample comprised 31 MS patients (excluding the primary progressive type), whose mean age was 37.58 years (SD = 8.51; range, 20 to 54 years), and 31 cadaveric liver transplant recipients (excluding hepato-renal and retransplantation cases), whose mean age was 45.35 years (SD = 11.11; range, 22 to 59 years). The groups were matched for gender (22 women and 9 men). The general inclusion criteria were: a cognitive level allowing completion of the questionnaire and not having suffered a recent loss of a relative. We excluded MS patients with other neurological comorbid conditions, or with a relapse within 2 months before assessment. The MS treatment consisted of Natalizumab. The three kinds of drugs for transplant recipients were: mycophenolate mofetil (10% of transplant recipients, n = 3), cyclosporine plus mycophenolate mofetil (29%; n = 9), or tacrolimus plus mycophenolate mofetil (61%; n = 19). Our Ethics and Health Research Commission approved this investigation, and written informed consent was obtained from all participants. We used Spanish version of the SF-36 Health Survey.[6] Analysis of covariance was computed for each group to control for the time from MS diagnosis or transplantation surgery to assessment. Student *t* test for unpaired samples of covariate-adjusted mean values was used as statistical index, and Cohen's *d*s were calculated to assess the size of intergroup differences and the clinical significance between patients and a representative age-adjusted sample (18 to 64 years old) of the general Spanish population (n = 7881).[7] Data were analyzed with IBM-SPSS 19.0 statistical software package (SPSS, Inc., Chicago, Ill) for Windows PC.

RESULTS

We previously verified that no significant difference in the SF-36 subscales was related to immunosuppressants pre-



	Bodily pain	Role-physical	Mental health	General health	Vitality	Social functioning	Role-emotional	Physical functioning
t(60)	0.11	2.12	1.64	3.09	2.17	1.56	0.79	2.01
P	.913	.038*	.107	.003*	.034*	.124	.431	.049*
$d_{1\text{-}2}$	-0.028 -	-0.539 M	-0.416 S	-0.785 M	-0.552 M	-0.397 S	-0.201 S	-0.511 M
$d_{1\text{-}3}$ †	-0.787 M	-0.699 M	-0.334 S	-0.683 M	-0.569 M	-0.919 L	-0.736 M	-0.974 L
$d_{2\text{-}3}$ †	-0.846 L	-1.239 L	-0.858 L	-1.760 L	-1.181 L	-1.467 L	-1.015 L	-1.545 L

d: Cohen's *d*. Effect sizes: -, null; S, small; M, medium; L, large; * $P < .05$
† Computations for clinical significance

Fig 1. Adjusted means on quality of life (SF-36) among liver transplantation and multiple sclerosis patients and means from the age-adjusted general Spanish population (the lower score, the worse quality of life).

scribed to transplant recipients: bodily-pain (F[2,28] = 0.788, $P = .465$), role-physical (F[2,28] = 0.175, $P = .841$), mental health (F[2,28] = 0.250, $P = .780$), general health (F[2,28] = 0.048, $P = .953$), vitality (F[2,28] = 0.254, $P = .778$), social functioning (F[2,28] = 1.001, $P = .380$), role-emotional (F[2,28] = 0.110, $P = .896$), and physical functioning (F[2,28] = 0.022, $P = .978$). Figure 1 shows significantly worse scores among neurological patients compared with liver transplant recipients regarding role-physical ($P = .038$), general health ($P = .003$), vitality ($P = .034$), and physical functioning ($P = .049$), with medium effect sizes (Cohen's *d*s from −0.511 to −0.785). Against normative values, liver transplant recipients achieved relevant differences in all SF-36 subscales (Cohen's *d*s from −0.569 to −0.974) except for mental health (Cohen's *d*: −0.334, small effect size). Likewise, MS patients showed much greater differences (Cohen's *d*s from −0.846 to −1.760) versus the reference group.

DISCUSSION

This study sought to compare the QoL between two clinical groups controlling for the time from diagnosis/transplant surgery until the assessment because this variable has been reported to predict QoL.[8–10] Relevant differences (large and medium effect sizes) were observed in both medical conditions against normative values. In line with other studies,[8,11] the scores were clinically significant in most QoL domains: bodily pain; role and social activity limitations due to physical and emotional problems (role-physical, role-emotional, and social functioning); vitality; general health; as well as basic and instrumental activities of daily living (physical functioning). Only liver transplant recipients showed a level approaching that of the reference population in mental health as has been reported repeatedly.[8,9] Regarding the comparison between patients, liver transplant recipients enjoyed better QoL than MS patients. The greatest differences were observed in the SF-36 physical subscales (role-physical, physical functioning, and vitality) due to the neurodegenerative nature of MS. Consistently, the neurological patients showed much worse self-perceived general health. Similarly, the self-perceptions of global health status showed coherence with other medical parameters in other studies.[11,12] We concluded that transplant recipients belong to a population that still requires special health care because, even after having undergone the treatment of choice to overcome their liver disease, they show clinically significant impairments in most major dimensions of biopsychosocial functioning.

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10.2. Separata del artículo titulado "*Evolution of quality of life in renal transplant recipients and patients with multiple sclerosis: A follow-up study*"

Evolution of Quality of Life in Renal Transplant Recipients and Patients With Multiple Sclerosis: A Follow-up Study

E. Fernández-Jiménez, M.A. Pérez-San-Gregorio, A. Martín-Rodríguez, J. Pérez-Bernal, and G. Izquierdo

ABSTRACT

Objective. We aimed to compare the evolution of quality of life in 2 medical conditions under immunotherapy (cadaveric renal transplantation [G_1] and multiple sclerosis [G_2]), and to assess the clinical significance of the results compared with a representative age-adjusted sample of the general Spanish population (G_3).

Methods. Using a mixed design (2×2), the SF-36 Health Survey was administered to 60 patients with one of these clinical conditions (30 in each group; the patient group factor), matched for gender, and homogenized regarding age and working status. All renal patients had undergone transplantation 6 months before the first assessment, and all neurological patients presented a relapsing-remitting course and a mild-moderate disability level. Both patient groups were assessed a second time 6 months later (the phase factor). A mixed analysis of covariance was computed controlling for age as a covariate. Cohen's d was reported as an effect size index and to analyze the clinical significance regarding a representative age-adjusted sample of the general Spanish population ($n = 5821$).

Results. Statistically significant differences were found between patient groups in vitality, bodily pain, social functioning, and mental health ($P < .01$), in which worse levels were displayed by patients with multiple sclerosis in both phases (Cohen's $ds_{1\text{-}2}$ from 0.61 to 1.40). Likewise, an interactive effect was observed in physical functioning [$F(1,57) = 12.93$; $P = .001$], such that the performance of daily physical activities improved in renal recipients after 6 months, but it decreased in neurological patients. Patients with multiple sclerosis showed higher, clinically significant impairment in all SF-36 dimensions in both phases compared with renal recipients (Cohen's $ds_{2\text{-}3}$ from -0.50 to -1.61), who presented clinically significant impairment in general health, role-physical, and role-emotional (Cohen's $ds_{1\text{-}3}$ from -0.73 to -1.28).

Conclusions. Renal transplant recipients need specialized health care 1 year after transplantation because they still display relevant impairment in daily functioning compared with the general population.

THE COMPARISON of quality of life (QoL) between renal transplant recipients and other patient populations would allow determination of the relative impact of these clinical conditions on QoL.[1] Nevertheless, only a longitudinal study design would permit drawing more decisive conclusions than those from a cross-sectional study. This can be

From the Faculty of Psychology, Department of Personality, Assessment, and Psychological Treatments (E.F.-J., M.A.P.-S.-G., A.M.-R.), University of Seville, Spain; Critical Care and Urgencies (J.P.-B.), University Hospital Virgen del Rocío of Seville, and the Multiple Sclerosis Unit (G.I.), University Hospital Virgen Macarena, Seville, Spain.

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Address reprint requests to Eduardo Fernández-Jiménez, Facultad de Psicología, Departamento de Personalidad, Evaluaci ón y Tratamiento Psicológicos, C/ Camilo José Cela, s/n, 41018, Sevilla, Spain. E-mail: eduferjim2@us.es

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Table 1. Adjusted Means of QoL (SF-36) in Renal Transplant Recipients and Patients With MS Between Time Points, and Clinical Significance Compared With the Age-Adjusted General Spanish Population (Lower Scores Represent Worse QoL)

	First Phase					6 Months Later					Main Effects		Interactive Effects
SF-36 subscales	Renal transplant M^{*}_{G1} (*SD*)	MS patients M_{G2} (*SD*)	$d_{G1\text{-}G2}$†	$d_{G1\text{-}G3}$	$d_{G2\text{-}G3}$	Renal transplant M_{G1} (*SD*)	MS patients M_{G2} (*SD*)	$d_{G1\text{-}G2}$	$d_{G1\text{-}G3}$	$d_{G2\text{-}G3}$	Group *F*(1,57) (*P*)	Phase *F*(1,57) (*P*)	*F*(1,57) (*P*)
Role-physical	52.92 (30.39)	63.62 (30.39)	−0.35 S	−1.05 L	−0.71 M	59.19 (28.64)	59.35 (28.64)	−0.01 –	−0.87 L	−0.87 L	0.70 (.406)	0.59 (.448)	1.74 (.193)
Bodily pain	87.47 (25.32)	53.36 (25.32)	1.35 L	0.25 S	−1.06 L	83.58 (27.03)	57.09 (27.03)	0.98 L	0.10 –	−0.88 L	28.70 (.001)	0.60 (.443)	1.06 (.308)
General health	43.83 (22.13)	43.17 (22.13)	0.03 –	−1.28 L	−1.31 L	46.55 (19.90)	41.78 (19.90)	0.24 S	−1.21 L	−1.45 L	0.34 (.565)	0.34 (.565)	0.56 (.458)
Vitality	71.26 (22.45)	39.91 (22.45)	1.40 L	0.11 –	−1.33 L	67.02 (19.58)	44.98 (19.58)	1.13 L	−0.09 –	−1.17 L	35.49 (.001)	0.40 (.530)	2.28 (.136)
Social functioning	78.63 (26.95)	62.20 (26.95)	0.61 M	−0.59 M	−1.31 L	81.97 (29.53)	62.20 (29.53)	0.67 M	−0.41 S	−1.22 L	9.23 (.004)	0.01 (.912)	0.16 (.694)
Role-emotional	67.01 (32.03)	69.00 (32.03)	−0.06 –	−0.79 M	−0.72 M	69.18 (30.57)	67.10 (30.57)	0.07 –	−0.73 M	−0.81 L	0.00 (.995)	0.07 (.793)	0.18 (.675)
Mental health	78.31 (21.60)	59.55 (21.60)	0.87 L	0.20 S	−0.71 M	76.90 (19.91)	64.27 (19.91)	0.63 M	0.14 –	−0.50 M	11.88 (.001)	0.13 (.721)	1.17 (.284)

Abbreviations: G1: renal transplant; G2: multiple sclerosis; G3: general Spanish population.
*Means adjusted for age.
†Cohen's *d* index: -, null effect size; S, small effect size; M, medium effect size; L, large effect size.

Table 2. Simple Effects Regarding Physical Functioning (SF-36) in Renal Transplant Recipients and Patients With MS Between Time Points, and Clinical Significance Compared With the Age-Adjusted General Spanish Population

Physical functioning Simple effects	*P*	$d_{G1\text{-}G2}$*	$d_{G1\text{-}G3}$	$d_{G2\text{-}G3}$
Renal transplant	.026	−0.31 S		
First phase				
6 mo later				
Patients with MS	.007	0.38 S		
First phase				
6 mo later				
First phase	.005	0.76 M	−0.51 M	−1.30 L
Renal transplant				
Patients with MS				
6 mo later	.001	1.32 L	−0.16 –	−1.61 L
Renal transplant				
Patients with MS				

Main effects		Interactive Effect
Group *F*(1,57), *P*	Phase *F*(1,57), *P*	*F*(1,57), *P*
19.20, .001	1.34, .252	12.93, .001

G1: renal transplant; G2: multiple sclerosis; G3: general Spanish population.
*Cohen's *d* index: -, null effect size; S, small effect size; M, medium effect size; L, large effect size.

approached by 2 procedures: (1) comparing renal to other organ transplant recipients, which has been widely performed[2]; or (2) contrasting renal recipients with other chronic conditions unrelated to the transplantation process. This latter has scarcely been studied[1] and would allow analyzing whether the impairments identified are due to the transplantation itself or to chronic condition-related stressors. Ideally, the other illness condition should share some similarities with the transplant group (eg, its immunocompromised nature), hence multiple sclerosis (MS) is a suitable comparison condition.[3] This is the first study with the aims of comparing QoL evolution in 2 medical conditions under immunotherapy (cadaveric renal transplant recipients [G_1] and MS patients [G_2]), and assessing the clinical significance of the results compared with a representative age-adjusted sample of the general Spanish population (G_3).

METHODS

Selection and Description of Participants and Statistical Techniques

Sixty patients with one of these clinical conditions were assessed (30 patients in each group: the patient group factor), matched for gender (15 females in each group) and homogenized with regard to age (mean$_{G1}$ [M_{G1}] = 40.23 years, standard deviation$_{G1}$ [SD_{G1}] = 10.15 and M_{G2} = 39.57 years, SD_{G2} = 9.27; F (1,59) = 0.07; P = .791) and working status [χ^2 (2,59) = 1.62; P = .444]. The general inclusion criteria were as follows: a cognitive level allowing completion of the questionnaire, not having suffered a recent loss of a relative, and being treated with immunosuppressive drugs/immunomodulators. The specific exclusion criteria were as follows: hepato-renal and retransplantation cases, patients with

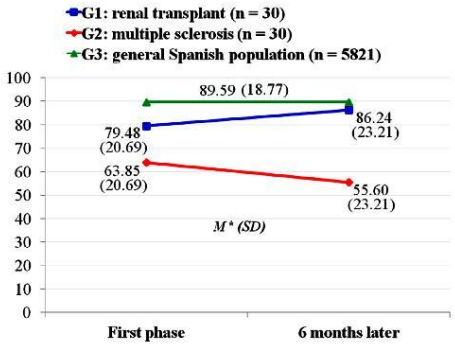

Fig 1. Adjusted means of physical functioning (SF-36) in renal transplant recipients and patients with MS between time points compared with mean of the age-adjusted general Spanish population (lower scores represent worse QoL). *Means adjusted for age (SD).

MS with other comorbid neurological conditions, and an MS relapse during the 2 months prior to the assessment. The Spanish version of the SF-36 Health Survey was used. All renal patients had undergone transplantation 6 months before the first assessment phase, and all patients with MS presented a relapsing-remitting course and a mild-moderate disability level measured by the Expanded Disability Status Scale (EDSS; from 1.0 to 5.5). Both patient groups were assessed a second time 6 months later (the phase factor). Our Research Ethics Commissions approved this investigation, and written informed consent was obtained from all participants. A mixed analysis of covariance (2 × 2 design) was computed, controlling for age as a covariate. Cohen's *d* was reported as an effect size index, as well as to analyze the clinical significance of the results regarding a representative age-adjusted sample (25 to 64 years old) of the general Spanish population (n = 5821).[4] Data were analyzed with IBM-SPSS 19.0 statistical software package (SPSS, Inc., Chicago, Ill, United States) for Windows PC.

RESULTS

Time since MS diagnosis (M = 108.03 months; SD = 82.20) was unrelated to any QoL subscale (Pearson's correlations [$rs_{pearson}$] from –0.008 to .298). A main effect of the patient group factor was statistically significant in vitality, bodily pain, social functioning, and mental health (Table 1), in which worse levels were displayed by patients with MS compared with renal transplant recipients in both assessment phases (Cohen's $ds_{1\text{-}2}$ from 0.61 to 1.40). Likewise, a statistically significant interactive effect was observed in physical functioning (F[1,57] = 12.93; P = .001; Table 2), such that the performance of daily physical activities improved in renal transplant patients after 6 months, but it decreased in patients with MS (Fig 1). However, the main effect of the patient group factor was greater in physical functioning (F[1,57] = 19.20; P = .000) than the interactive effect, ie, differences between clinical conditions were more relevant regardless of the study phase (Cohen's $ds_{1\text{-}2}$ = 0.76 and 1.32, in the first and second phase, respectively). No relevant differences were observed between time points regarding the remaining QoL dimensions in either patient group (null and small effect sizes). Patients with MS showed higher, clinically significant impairment in all QoL dimensions, in both phases (Cohen's $ds_{2\text{-}3}$ from −0.50 to −1.61), in comparison with renal transplant recipients, who reached normative levels in vitality, bodily pain, and mental health in both assessment phases (Cohen's $ds_{1\text{-}3}$ from −0.09 to 0.14).

DISCUSSION

Renal transplant recipients showed a better QoL, in terms of daily physical activities, vitality, pain, social functioning, and mental health, than patients with MS, at both 6 and 12 months after having undergone transplantation. Although MS patients were in remission and they presented a mild-moderate disability level, their impairment was clinically significant in all QoL dimensions in both phases. Overall, both medical conditions retained similar levels of biopsychosocial functioning after 6 months,[2,5] although renal recipients presented a trend to improvement in basic and instrumental activities of daily living, reaching normative levels at that time. However, these renal recipients still showed clinically significant deterioration in terms of general health status and daily activity limitations due to physical and emotional problems. This latter impairment (role-emotional) contrasts with their nonclinical levels in negative affectivity (mental health subscale), which may be being amplified, thereby limiting their daily functioning, due to the interaction with other concurrent factors (eg, demanding medical treatment). Thus, this population continues to require specialized health care 1 year after undergoing transplantation because they still show relevant difficulties in daily functioning due to their health problems, compared with the general population.

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We want to thank all the team from the University Hospital Virgen Macarena as well as Dr Gemma Vilagut Saiz for having provided the age-adjusted SF-36 means of the general Spanish population.

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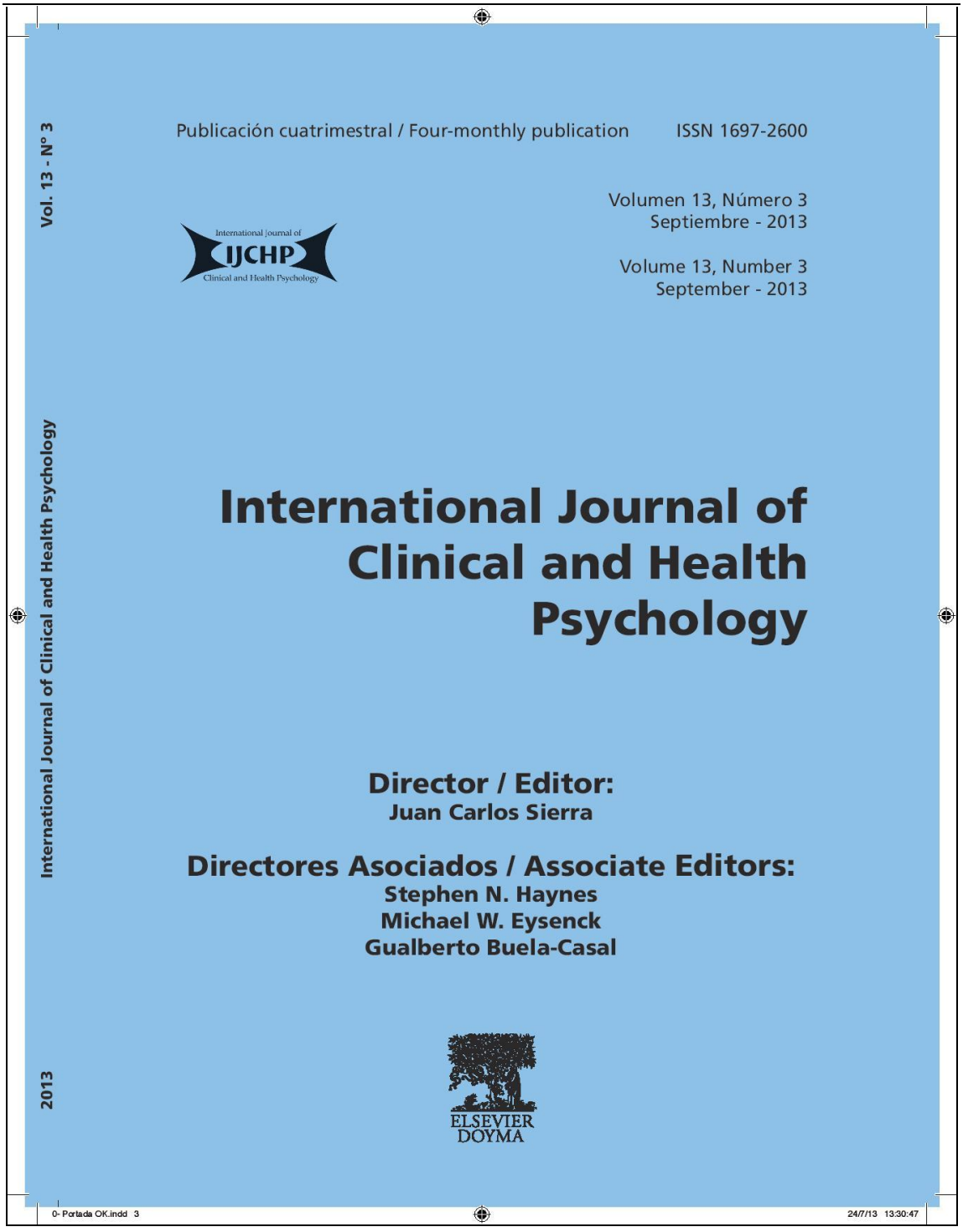
10.3. Separata del artículo titulado "*Psychometric properties of a revised Spanish 20-item Toronto Alexithymia Scale adaptation in multiple sclerosis patients*"



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ORIGINAL ARTICLE

Psychometric properties of a revised Spanish 20-item Toronto Alexithymia Scale adaptation in multiple sclerosis patients

Eduardo Fernández-Jiménez[a,*], María Ángeles Pérez-San-Gregorio[a], Graeme J. Taylor[b,c], R. Michael Bagby[b,d], Lindsay E. Ayearst[b], Guillermo Izquierdo[e]

[a]*Universidad de Sevilla, Spain*
[b]*University of Toronto, Canada*
[c]*Mount Sinai Hospital, Canada*
[d]*Centre for Addiction and Mental Health, Canada*
[e]*Hospital Universitario Virgen Macarena, Spain*

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KEYWORDS
20-item Toronto Alexithymia Scale;
Factorial validity;
Multiple sclerosis;
Prevalence;
Instrumental study

Abstract There have been a small number of investigations of alexithymia in multiple sclerosis (MS) using the 20-item Toronto Alexithymia Scale (TAS-20). However, the TAS-20 factor structure has not yet been evaluated in a MS patient sample, and earlier Spanish translations of this instrument require some improvement. We aimed to evaluate the factorial validity and reliability of an improved Spanish translation of the TAS-20 (the TAS-20-S). The TAS-20-S was completed by 221 MS patients. Confirmatory factor analysis was used to compare the fit of six different factor models. Internal consistency and retest reliability coefficients were also computed. The correlated three-factor model and the higher-order factor model made up of *Difficulty Identifying Feelings*, *Difficulty Describing Feelings*, and *Externally Oriented Thinking* achieved the best fit. Alpha coefficients ranged between .87 and .67; mean inter-item correlations ranged between .48 and .20; and retest correlations after 6 months ranged between .61 and .52. A high degree of alexithymia was present in 18.1% of the sample. Reliability and the traditional three-factor structure were demonstrated for the TAS-20-S, which can now be recommended for assessing an aspect of emotional processing in MS patients.

PALABRAS CLAVE
Escala de Alexitimia de Toronto;
Validez factorial;
Esclerosis múltiple;

Resumen En la esclerosis múltiple (EM) son escasas las investigaciones centradas en evaluar la alexitimia con la Escala de Alexitimia de Toronto (TAS-20). A pesar de ello, no se ha evaluado aún su estructura factorial en dicha población y, además, las anteriores traducciones al español necesitan modificaciones. Los objetivos del presente estudio fueron evaluar la validez factorial y la fiabilidad de una traducción mejorada en español de la TAS-20 (la TAS-20-S), la cual fue administrada en una muestra de 221 pacientes con EM. Se realizaron análisis factoriales confir-

*Corresponding author at: Facultad de Psicología, Departamento de Personalidad, Evaluación y Tratamiento Psicológicos, C/ Camilo José Cela s/n, 41018, Sevilla, Spain.
E-mail address: eduferjim2@us.es (E. Fernández-Jiménez).

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Prevalencia;
Estudio instrumental

matorios para comparar el ajuste de seis modelos factoriales. También se calcularon coeficientes de consistencia interna y de fiabilidad test-retest. Los modelos trifactorial correlacionado y el de orden superior conformados por *Dificultad en Identificar Sentimientos*, *Dificultad en Describir Sentimientos* y *Pensamiento Externamente Orientado* lograron el mejor ajuste. Los coeficientes alfa oscilaron entre 0,87 y 0,67; las correlaciones medias inter-ítem entre 0,48 y 0,20; y las correlaciones test-retest tras 6 meses oscilaron entre 0,61 y 0,52. El 18,10% de la muestra presentó niveles elevados de alexitimia. La TAS-20-S presentó una adecuada fiabilidad así como la tradicional estructura trifactorial, por lo que su uso es ahora recomendable para evaluar un aspecto del procesamiento emocional en EM.

Alexithymia is a multifaceted dimensional personality construct that reflects a disturbance in affective information processing and social-cognitive functioning (Taylor & Bagby, 2012; Wingbermühle, Theunissen, Verhoeven, Kessels, & Egger, 2012). This construct encompasses difficulties in identifying subjective feelings and differentiating between feelings and the somatic sensations associated with emotional arousal, difficulty verbalizing emotional feelings to others, a restricted imaginal capacity, and an externally-oriented style of thinking (Taylor, Bagby, & Parker, 1997). There may also be associated impairments in recognizing emotions in human facial expressions, as demonstrated in studies with healthy volunteers (Kano, Fukudo, & Gyoba, 2003) and multiple sclerosis patients (Prochnow et al., 2011).

Despite empirical evidence that alexithymia, and other related concepts, are associated with a wide variety of medical and psychopathological disorders and symptomatology (Balluerka, Aritzeta, Gorostiaga, Gartzia, & Soroa, 2013; Pascual, Etxebarria, Cruz, & Echeburúa, 2011; Taylor & Bagby, 2012; Taylor et al., 1997), the construct has been scarcely investigated in multiple sclerosis (MS). This is somewhat surprising given recent findings that this personality trait is a strong predictor of the most quality-of-life disabling condition in MS, namely, depression (Bodini et al., 2008; Feinstein, 2011; Gay, Vrignaud, Garitte, & Meunier, 2010). The strong association between depression and alexithymia in MS might be explained partly by evidence that negative emotions are processed predominantly by neocortical areas in the right hemisphere (Adolphs, Jansari, & Tranel, 2001), which have been found to show reduced activation in response to emotional stimuli in individuals with high degrees of alexithymia (Kano et al., 2003), thereby contributing to deficits in the cognitive processing and regulation of negative affects.

The objectives of the few empirical studies that assessed alexithymia in MS patients were to identify the facets of the construct that are most relevant to MS (Bodini et al., 2008; Chahraoui et al., 2008; Gay et al., 2010), and to estimate the prevalence of alexithymia among MS patients, although the samples in these studies were small in size (58 to 115 patients). In pursuing these objectives, alexithymia was measured with the 20-item Toronto Alexithymia Scale (TAS-20) (Bagby, Parker, & Taylor, 1994), which is the most frequently and widely-used instrument for assessing the construct (Taylor & Bagby, 2012). This self-report scale is comprised of three factor scales that assess difficulty identifying feelings, difficulty describing feelings to others, and externally-oriented thinking. The TAS-20 has been translated into more than 24 different languages, and validated in clinical and/or nonclinical samples in Western, Eastern-European, East-Asian, and Middle-Eastern countries (Taylor & Bagby, 2012; Taylor, Bagby, & Parker, 2003).

To our knowledge, there are three existing Spanish adaptations of the TAS-20, two of which were developed in Latin-American countries - Mexico (Pérez-Rincón et al., 1997) and Peru (Loiselle & Cossette, 2001) - and one developed in Spain (Martínez-Sánchez, 1996; Páez et al., 1999). These adaptations of the scale have certain limitations. For example, the Mexican and Peruvian versions present some dialectical particularities when compared with the Spanish spoken in Spain. In addition, the Latin-American versions, and also the version developed in Spain, contain some items whose back-translation does not adequately reflect the meanings of the original English version of the items. Moreover, the indices and criteria used to evaluate goodness of fit of the three-factor model of the Spanish translations of the TAS-20 do not meet the standards that are currently employed in psychometric studies and recommended in Hu and Bentler's (1999) guidelines.

Some investigators have obtained a different factor structure for the TAS-20 in studies with patient samples (Kooiman, Spinhoven, & Trijsburg, 2002; Müller, Bühner, & Ellgring, 2003; Pérez-Rincón et al., 1997), suggesting that the factor structure might depend on the specific sample analyzed. Although a few studies have used the TAS-20 to assess alexithymia in MS patients, the reliability and three-factor structure of the scale have not yet been evaluated in this population. It is important to address this deficiency not merely to satisfy professionals in the measurement field (Carretero-Dios & Pérez, 2007), but also for clinical reasons as evidence for the validity of the scale will allow researchers to identify which of the TAS-20 factor scales are differentially related to other clinical outcomes in a more meaningful way (Briggs & Cheek, 1986). There is evidence, for example, that the *Difficulty Identifying Feelings* factor scale of the TAS-20 is stronger than the total scale in predicting fatigue and depression in MS patients (Bodini et al., 2008).

Given the above considerations, the aim of this instrumental study (Montero & León, 2007) was to work collaboratively with the developers of the original English

version of the TAS-20 to develop a revised and improved Spanish translation of the scale, and to evaluate its reliability and factor structure in a sample of patients with MS. This is the first study to assess alexithymia in a Spanish MS sample.

Method

Participants

Two hundred and sixty-five outpatients with MS who came for their routine medical checkups at the University Hospital Virgen Macarena in Seville, Spain, were invited to participate in this study in 2011. However, 44 patients were not enrolled because they declined (14 patients) or lacked time to participate (7 patients); or because of the following exclusion criteria: cognitive impairment (13 patients); neurological comorbid conditions (5 patients); major psychiatric disorders (1 patient with chronic psychosis) or a significant mood disturbance at the time of assessment (2 patients); and other special conditions (2 patients pregnant). The final sample was comprised of 221 participants (83.4%), who were all diagnosed with multiple sclerosis according to the 2010 revised McDonald's criteria (Polman et al., 2011). The participants were involved through the convenience sampling technique. Sociodemographic data and information about the course of MS, functional disability according to the Expanded Disability Status Scale (EDSS), and pharmacotherapy were collected. The clinical and sociodemographic characteristics are presented in Table 1.

Instruments

The TAS-20 is a 20-item self-report instrument with each item scored on a 5-point Likert scale (Bagby et al., 1994). Total scores range between 20 and 100 with higher scores indicating greater degrees of alexithymia. The developers of the scale recommend the following empirically established cutoff scores: nonalexithymic cases: ≤ 51; borderline cases: 52-60; alexithymic cases: ≥ 61 (Taylor et al., 1997). The English version of the TAS-20 was adapted to the Spanish language in an iterative-process (Carretero-Dios & Pérez, 2005). First, the original English version was translated into Spanish by several university researchers in the field of clinical psychology, and with expertise in construction and adaptation of questionnaires, who also reviewed the existing Spanish adaptations of the TAS-20 and made corrections to items they thought had been inadequately translated. For example, a frequent mistake in translation was the use of "explain feelings" as a synonym for "describe feelings" when both verbs differentiate between a deeper emotional processing - analyze or explain - against a lighter one - describe -, and precisely the latter was the alexithymic characteristic of interest. Given the importance of reviewing the adequacy of a translation with statistical methods (Sireci, Yang, Harter, & Ehrlich, 2006), the new Spanish translation of the TAS-20 was also influenced by considering the inadequate psychometric functioning of some items in the earlier Spanish versions. Second, a Spanish-English bilingual PhD psychologist, who was familiar with the Spanish and American cultures but not given access to the original English version of the TAS-20, made a back-traslation of the new Spanish translation. Finally, this back-translated English version was then reviewed and compared with the original English version by the developers of the TAS-20. Moreover, a bilingual research assistant working in Canada also compared this back-translation with the Spanish version. Some further modifications were made until a consensus was reached about the final translation. The final Spanish adaptation of the scale (the TAS-20-S) was then pilot tested with 20 patients; the items were read to them to check if the items were correctly understood and to identify any difficulties in answering them. Only 8 items remained with the same or similar translation to the first version of the TAS-20 adapted in Spain.

Procedure

All patients were assessed individually by a trained psychologist (EFJ) during their routine checkups at the hospital after written informed consent was obtained. The TAS-20-S items were read by such psychologist, a method that has been used in other studies (Pérez-Rincón et al., 1997), given the MS patients' difficulties in understanding some of the items when they read the questionnaires by themselves. This procedure allowed us to avoid response tendencies and the problems with negatively-worded items reported in other studies (Loiselle & Cossette, 2001). The writing of this manuscript has followed the Hartley's (2012) guidelines. The study was approved by the Ethics Commission of Research of the University Hospital Virgen Macarena.

Data analysis

Confirmatory factor analyses were conducted using the matrix of polychoric correlations, as was carried out in other studies (Gorostiaga, Balluerka, Aritzeta, Haranburu, & Alonso-Arbiol, 2011), with Weighted Least Squares Means and Variances (WLSMV) estimation (Flora, LaBrish, & Chalmers, 2012). The goodness-of-fit indices computed and presented according to Hammervold and Olsson's (2012) classification were as follows: chi-square goodness-of-fit index; Weighted Root Mean Square Residual (WRMR) was selected as a measure of *absolute fit* and *residual-based fit*; the Tucker-Lewis Index (TLI) and the Comparative Fit Index (CFI) were selected as measures of *incremental fit*; and the Root-Mean-Square Error of Approximation (RMSEA) along with its 90% confidence interval was chosen as a measure of *parsimonious fit*. All these indices were interpreted simultaneously to overcome the limitations of each one (Carretero-Dios & Pérez, 2005; Hammervold & Olsson, 2012). The following standards were used to assess the model fit: a non-significant value of chi-square; WRMR ≤ 1 (Yu, 2002); TLI and CFI ≥ .90 (Marsh, Hau, & Wen, 2004); and RMSEA < .08 (MacCallum, Browne, & Sugawara, 1996). Each of the TAS-20 items was specified as an indicator of only a single factor.

The following six different factor models were tested and compared:

1) A unidimensional model in which all items load on one unique factor (Lambert et al., 1999).

Table 1 Clinical and sociodemographic characteristics of the multiple sclerosis patients (n = 221).

	Mean *(SD)*
Age (in years)	40.61 (9.65)
Months since diagnosis	101.43 (75.28)
Expanded Disability Status Scale (EDSS)	3.04 (1.83)
	% (n)
EDSS 0	4.10 (9)
Mild EDSS level (1-3.5)	61.50 (136)
Moderate EDSS level (4-6.5)	30.80 (68)
Severe EDSS level (> 7)	3.60 (8)
Multiple sclerosis course	
Relapsing remitting	77.80 (172)
Secondary progressive	17.70 (39)
Primary progressive	4.50 (10)
Disease modifying therapy: yes/no	76.90 / 23.1 (170 / 51)
Antidepressant medication: yes/no	27.10 / 72.9 (60 / 161)
Anxiolytic medication: yes/no	25.80 / 74.2 (57 / 164)
Female/male gender	63.03 / 36.7 (140 / 81)
Marital status	
Partner (married or stable relationship)	78.30 (173)
Single	14.09 (33)
Separated/divorced	5.90 (13)
Widow	0.90 (2)
*Educational level**	
High	549.50 (110)
Secondary	29.90 (66)
Primary	20.4 (45)
Employment status	
Permanent/transient disability	35.30 (78)
Working	34.40 (76)
Unemployed/students	15.4 (34)
Sick leave	7.20 (16)
Adapted work	2.30 (5)
Housewives	1.80 (4)
Retired	0.50 (1)

*High level: completed university or a high level vocational training program; Secondary level: completed high school or a medium level vocational training program; Primary level: did not complete high school.
Note. SD = standard deviation.

2) An oblique two-factor model in which *Difficulty Identifying Feelings* (DIF) and *Difficulty Describing Feelings* (DDF) belong to the same factor (DIDF) and *Externally Oriented Thinking* (EOT) is isolated in another factor (Kooiman et al., 2002; Pérez-Rincón et al., 1997).

3a) The traditional oblique three-factor model made up of DIF, DDF and EOT, according to the developers of the TAS-20 (Bagby et al., 1994).

3b) A comparable hierarchical model was also tested in which DIF, DDF, and EOT were specified to indicate a second-order factor: *Global Alexithymia*.

3c) An alternative oblique three-factor model with DIF and DDF belonging to the same factor (DIDF); and EOT divided into two separate factors: *Pragmatic Thinking* (PR) - items 5, 8 and 20 - and *Lack of Importance of Emotions* (IM) - items 10, 15, 16, 18, and 19 (Müller et al., 2003).

4) An oblique four-factor model with DIF, DDF, PR and IM as separate factors (Müller et al., 2003).

To assess internal consistency reliability of the TAS-20-S, alpha coefficients and mean inter-item correlations (MICs) were computed for the best fitting factor model. A standard of .70 or higher was set for alpha coefficients and an optimal range of .20 to .40 for MICs (Briggs & Cheek, 1986). Finally, 85 of the participants were enrolled to evaluate retest reliability; these patients completed the TAS-20-S approximately 6 months (M = 5.70 months, SD = 0.99) after its initial administration. No missing data were found and no data transformations were carried out. All analyses were conducted with the program Mplus 6.1 (Muthén & Muthén, 2011) and the IBM-SPSS 19.0 statistical software package (SPSS, Inc., Chicago, Ill) for Windows PC.

Table 2 Standardized factor loadings for each model.

	Model 1	Model 2		Model 3a			Model 3c			Model 4			
Item		DIDF	EOT	DIF	DDF	EOT	DIDF	PR	IM	DIF	DDF	PR	IM
1	.853	.857		.872			.857			.872			
3	.548	.554		.571			.555			.574			
6	.806	.812		.824			.812			.825			
7	.684	.692		.711			.692			.710			
9	.832	.838		.855			.838			.855			
13	.731	.738		.757			.738			.755			
14	.730	.735		.751			.736			.751			
2	.793	.799			.877		.799				.876		
4	.617	.623			.665		.622				.666		
11	.597	.601			.648		.600				.648		
12	.420	.419			.456		.418				.456		
17	.564	.563			.616		.562				.615		
5	.263		.454			.446		.418				.417	
8	.469		.710			.698		.650				.651	
10	.237		.459			.464			.497				.497
15	.207		.339			.348			.364				.369
16	.287		.463			.459			.488				.469
18	.391		.528			.543			.548				.559
19	.195		.405			.416			.444				.454
20	.406		.640			.634		.593				.593	

Note. DIDF = Difficulty Identifying Feelings together with Difficulty Describing Feelings; DIF = Difficulty Identifying Feelings; DDF = Difficulty Describing Feelings; EOT = Externally Oriented Thinking; PR = Pragmatic Thinking; IM = Lack of Importance of Emotions. All factor loadings are statistically significant, $p < .001$.

Results

No statistically significant differences were found between the participants in the study and the nonparticipants (n = 44) in the variables of age [$F_{(1, 263)} = 0.118$, $p = .731$], gender [$\chi^2_{(1, 265)} = 0.104$, $p = .747$], EDSS [$F_{(1, 53.711)} = 2.895$, $p = .095$], and number of months since MS diagnosis [$F_{(1, 263)} = 0.473$, $p = .492$].

In the participant sample, the mean total TAS-20-S score was 46.68 (SD = 14.38); alexithymic cases: 18.1% of sample (n = 40), mean 68.15 (SD = 5.24); borderline cases: 20.4% of sample (n = 45), mean 57.09 (SD = 2.73); nonalexithymic cases: 61.5% of sample (n = 136), mean 36.92 (SD = 7.63).

Confirmatory factor analysis

Factor loadings for each item across models are presented in Table 2. All items demonstrated statistically significant substantial loadings (≥ .30) on their specified factor across models, with the exception of model 1. In model 1, items 19, 15, 10, 5 and 16 failed to reach this minimal loading value. Correlations among factors across models are reported in Table 3. Correlations among factors were all moderate to large in size, ranging from .29 to .82. Based on the goodness-of-fit statistics evaluated (see Table 4), models 3a, 3b, and 4 achieved reasonable model fit. However, the specified higher-order model (3b) resulted in a small non-significant negative residual variance for DDF. Fixing this value to zero (resulting in a factor loading of 1.00) resulted in a reasonably fitting model that is nearly identical to the standard three-factor model (3a). All first-order coefficients were positive and statistically significant in this case,[1] and the second-order factor loadings for DIF and EOT were .79 and .56, respectively (all $p < .001$). Model 4 demonstrated a slightly better fit than models 3a and 3b; however, the correlation > 1.0 between IM and PR (also found in model 3c) is an indication that the two factors are not statistically distinguishable, making the results of this model inadmissible.[2] Overall, the standardized factor loadings from the traditional three-factor model (3a) were higher in the current study in comparison to those from the previous Spanish version of the TAS-20.

Reliability

Table 5 shows the MICs and alpha coefficients for the total TAS-20-S and three factor scales for the traditional three-factor model (3a). The MICs for the total scale and the DDF and EOT factor scales are in the recommended range of .20 to .40, indicating adequate item-to-scale homogeneity. Although the MIC for the DIF factor scale is outside this

[1]Due to space limitations and the fact that factor loadings of Model 3b were very similar to those of Model 3a, these coefficients are not shown in Table 2 and are available upon request.

[2]The correlation matrix is available upon request from the authors.

Table 3 Correlations among the factors.

	Model 2	Model 3a		Model 3c		Model 4		
	EOT	DDF	EOT	PR	IM	DDF	PR	IM
DIDF	.50			.58	.43			
DIF		.82	.41			.82	.54	.29
DDF			.61				.59	.63
EOT								
PR					1.04			1.03

Note. DIF = Difficulty Identifying Feelings; DDF = Difficulty Describing Feelings; EOT = Externally Oriented Thinking; PR = Pragmatic Thinking; IM = Lack of Importance of Emotions.
All correlations are statistically significant, $p < .001$.

Table 4 Goodness-of-fit indices of the factor models.

	1	2	3a	3b	3c	4
χ^2	599.683	440.767	388.316	388.821	437.819	370.562
df	170	169	167	168	167	164
p	< .001	< .001	< .001	< .001	< .001	< .001
RMSEA	.107	.085	.077	.077	.086	.075
90% confidence	.098-.116	.076-.095	.067-.088	.067 - .087	.076 - .096	.065-.086
CFI	.864	.914	.930	.930	.914	.935
TLI	.848	.904	.920	.921	.903	.924
WRMR	1.483	1.268	1.169	1.174	1.259	1.133

Note. RMSEA = Root Mean Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker Lewis Index; WRMR = Weighted Root Mean Square Residual.

Table 5 Alpha coefficients and mean inter-item correlations (MIC) for the 20-item Toronto Alexithymia Scale (TAS-20-S) and its factor scales (model 3a).

Factor scales	Cronbach's α	MIC	Retest reliability
DIF	.87	.48	$r = .52$, $p < .001$
DDF	.72	.34	$r = .61$, $p < .001$
EOT	.67	.20	$r = .56$, $p < .001$
TAS-20-S total	.86	.22	$r = .57$, $p < .001$

Note. DIF = Difficulty Identifying Feelings; DDF = Difficulty Describing Feelings; EOT = Externally Oriented Thinking.

optimal range, it is between .10 and .50, which is considered acceptable. The alpha coefficients range between .72 and .86 for the full scale and DIF and DDF factor scales, but for EOT the alpha coefficient is below the criterion of .70. The retest correlations for the full scale and three factor scales are all significant.

Discussion

In this pioneering study with a multiple sclerosis patient sample, our objectives were: a) to evaluate the factor structure of an improved Spanish translation of the TAS-20, which we named the TAS-20-S; and b) to evaluate the reliability of the TAS-20-S and its factor scales.

Regarding the first objective, the three-factor model of the TAS-20 was confirmed in the Spanish multiple sclerosis patient sample. The traditional correlated three-factor model and a higher-order factor model were the best fitting, both showing comparable results. Therefore, the factor scales *Difficulty Identifying Feelings*, *Difficulty Describing Feelings*, and *Externally Oriented Thinking* were replicated as core facets of the alexithymia construct assessed by the TAS-20 (Taylor et al., 2003). Although the use of externally imposed cutoff values to assess the goodness of fit of a model has been questioned - e.g.,

because the widely used Hu and Bentler's (1999) guidelines have sometimes been misinterpreted and considered too demanding - (Marsh et al., 2004), in the current study most goodness-of-fit indices for both three-factor models (3a and 3b) were adequate and acceptable. However, WRMR values were slightly above the criterion level of ≤ 1, and the chi-square goodness of fit was significant for all models. Although the four-factor model showed a slightly better fit, two factors (PR and IM) were statistically indistinguishable (correlation > 1). Therefore, the differentiation of the EOT factor into two separate factor scales was not justified in this sample in contrast to results obtained in some studies conducted with samples of patients with other diagnoses (Müller et al., 2003).

The current study included the recommended incremental fit indices (TLI and CFI), which were not computed in earlier confirmatory factor analytic studies of Spanish adaptations of the TAS-20 (Loiselle & Cossette, 2001; Páez et al., 1999). These indices are currently regarded as essential for assessing goodness of fit (Hu & Bentler, 1999) because TLI and CFI are relatively unaffected by sample size, and both detect model misspecification (Jackson, Gillaspy, & Purc-Stephenson, 2009). Although the CFI and TLI values in the MS patient sample did not reach the level of ≥ .95, which is considered acceptable according to Hu and Bentler's (1999) demanding guidelines, relaxing the criterion standard to ≥ .90 resulted in these fit indices indicating an adequate fit (Marsh et al., 2004). Moreover, the TLI and CFI values obtained in the current study exceed values reported in earlier studies for Dutch, Italian, Japanese, and Mandarin translations of the TAS-20 (Taylor et al., 2003; Zhu et al., 2007).

As was found when an improved Greek adaptation of the TAS-20 was developed (Tsaousis et al., 2010), the values of the goodness-of-fit indices for the TAS-20-S were better than those reported for earlier Spanish versions of the scale (Páez et al., 1999), and also supported the traditional three-factor model rather than a two-factor model (Pérez-Rincón et al., 1997). Moreover, regarding the three-factor model 3a, the factor loadings of 10 of the 12 items modified were higher in the current revised Spanish version in comparison to the first Spanish version of the TAS-20 administered to samples in Spain and Mexico (Martínez-Sánchez, 1996; Páez et al., 1999). This is consistent with other studies showing that the use of both judgmental and statistical techniques to ensure item comparability across languages can improve the psychometric properties of psychological measures (Sireci et al., 2006).

The estimates of internal consistency reliability were good for the total TAS-20-S and for the DIF and DDF factor scales, with particularly high alpha coefficients for DIF and the total scale. Although the alpha coefficient for the EOT factor scale was below the recommended standard of .70, and questionable according to George and Mallery (2003), the total scale and the DDF and EOT factor scales were within the optimal range of .20 to .40 for the mean inter-item correlations (MICs), which is a more appropriate index of a scale's cohesiveness (Briggs & Cheek, 1986). Moreover, the alpha coefficient for EOT was higher than has been reported for most other language adaptations of the TAS-20 (Taylor et al., 2003; Tsaousis et al., 2010; Zhu et al., 2007). Although the MIC for the DIF factor scale was outside the optimal range, it was less than .50, which is considered acceptable for multifactor scales (Briggs & Cheek, 1986). Thus all three factor scales of the TAS-20-S can be considered homogeneous, and can be scored along with the TAS-20-S total score in studies with MS populations.

Although retest reliability of the TAS-20-S was demonstrated over a 6-month interval, the correlations were lower in magnitude than those reported in other studies with medical patient samples and with a similar time interval between assessments. For example, the retest correlation of the total TAS-20 was .66 in a sample of women with breast cancer after a 6-month follow-up (Luminet, Rokbani, Ogez, & Jadoulle, 2007). The lower temporal stability of the TAS-20-S in the current study may possibly be accounted for by the neurodegenerative nature and variable course of MS.

The prevalence of alexithymic cases in this larger MS sample than previously investigated was 18.1% and 20.4% for borderline cases, which is in the range found in two other studies with MS patients - 13.8% in Italy (Bodini et al., 2008) and 23.2% in France (Gay et al., 2010) - using the same cut-off points. The prevalence rates of alexithymia are similar to the prevalence rates of depression in MS (Wood et al., 2013); hence the problems in emotional processing are not negligible in MS and neuropsychological interventions to address these impairments are required (Wingbermühle et al., 2012). Other research with various clinical populations has shown that treatments aimed at reducing alexithymia can result in better biopsychosocial outcomes (Beresnevaité, 2000; Melin, Thulesius, & Persson, 2010; Tulipani et al., 2010).

In conclusion, the results of the current study support the factorial validity of the TAS-20-S and indicate that it is a reliable instrument that can be used to assess an important aspect of emotional processing in MS populations. In particular, the scale might be used to investigate the clinical relevance of each of the three facets of the alexithymia construct in MS that may suggest a need for specific treatment interventions. Further research is needed to evaluate the psychometric properties of the TAS-20-S in community and other clinical samples, including assessment of the convergent and discriminant validity of the scale[3].

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[3]The TAS-20-S is available upon request from the authors.

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10.4. Hoja de información y consentimiento informado

CONSENTIMIENTO INFORMADO
INFORMACIÓN SOBRE LA INVESTIGACIÓN PARA EL POSIBLE PARTICIPANTE

Por favor, lea atentamente los siguientes apartados que explican los aspectos fundamentales del estudio titulado **"*Evolución biopsicosocial de los pacientes hepáticos durante el proceso de trasplante: análisis comparativo con la esclerosis múltiple*":**

- Los **objetivos** principales de este estudio son:

  -Evaluar y registrar diferentes variables psicológicas y médicas que repercuten en su estado de salud y en su calidad de vida: tipo de medicación prescrita, grado de discapacidad funcional, calidad de vida, dolor, dificultades en la expresión e identificación de sus emociones, sintomatología del estado de ánimo y ansiosa, etc.

  -Analizar la evolución biopsicosocial e identificar qué variables influyen en dicha evolución.

- Los resultados obtenidos en esta investigación servirán para transmitirlos a la comunidad científica (artículos en revistas científicas, ponencias en congresos, etc.), así como para la realización de una Tesis Doctoral.

- La **metodología** que vamos a emplear conlleva las siguientes fases:

  1. En una primera sesión, se administrarán una entrevista y una batería de tests psicológicos.
  2. Posteriormente, la evaluación se repetirá en diferentes momentos a lo largo de varios años (pasados 6 meses, pasados 18 meses, etc.).
  3. Los/as participantes serán seleccionados/as y evaluados/as, previo consentimiento escrito, por un único investigador, Eduardo Fernández Jiménez, becario de investigación del Programa de Formación de Profesorado Universitario (FPU) del Departamento de Personalidad, Evaluación y Tratamiento Psicológicos de la Facultad de Psicología de la Universidad de Sevilla (c/ Camilo José Cela s/n 41018 Sevilla), en fase de desarrollo de su Tesis Doctoral.

- **Confidencialidad:**

  - En cumplimiento de lo dispuesto en el artículo 5 de la Ley Orgánica 15/1999, del 13 de diciembre, de Protección de Datos de Carácter Personal (LOPD), **todos los datos recabados de los participantes serán tratados con absoluta confidencialidad**, no siendo revelados en modo alguno su identidad ni ningún indicio de la misma. Las únicas personas adicionales que tendrían acceso a ellos serían los investigadores colaboradores de este proyecto, pudiendo participar en las publicaciones científicas que se deriven de este estudio.

- De acuerdo a lo que establece la legislación mencionada, usted puede ejercer los derechos de acceso, modificación, oposición y cancelación de datos; para lo cual deberá dirigirse al investigador **Eduardo Fernández Jiménez**, quien será responsable de informarle y contestar a todas sus dudas. Usted podrá anular su decisión y retirar el consentimiento en cualquier momento, sin tener que dar explicaciones.

- Los datos recogidos en el estudio serán identificados mediante un código y sólo los investigadores del proyecto podrán relacionar dichos datos con su identidad, permaneciendo ésta en todo momento anónima.

- Una vez que haya leído todos estos puntos pregúnteme cualquier duda o aclaración que quiera saber sobre el estudio.

- Cuando tenga claro en lo que consiste el estudio, si desea participar en el mismo, exprese su consentimiento indicando su nombre y firmando al final del siguiente cuadro:

Título de la investigación: **"*Evolución biopsicosocial de los pacientes hepáticos durante el proceso de trasplante: análisis comparativo con la esclerosis múltiple*":**

Yo (nombre y apellidos),……

He leído la hoja de información que se me ha entregado.
He podido hacer preguntas sobre el estudio.
He recibido suficiente información sobre el estudio.
He hablado con el investigador del estudio, Eduardo Fernández Jiménez.
Comprendo que mi participación es voluntaria.
Comprendo que puedo retirarme del estudio:

1. Cuando quiera.
2. Sin tener que dar explicaciones.
3. Sin que esto repercuta, de manera alguna, en mis cuidados psicológicos o en mi atención sanitaria.

PRESTO LIBREMENTE MI CONFORMIDAD para participar en el estudio.

Fecha: Firma del participante: Firma del investigador: