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REPETICIÓN-IMITACIÓN Y AFASIA: BASES NEURALES Y TRATAMIENTO

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REPETITION-IMITATION AND APHASIA: NEURAL BASIS AND TREATMENT

Irene de Torres García

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UNIVERSIDAD
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Departamento de Medicina y Dermatología

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CERTIFICA:

Que Dña. *Irene de Torres García* ha realizado bajo su dirección el trabajo "REPETICIÓN-IMITACIÓN Y AFASIA: BASES NEURALES Y TRATAMIENTO", que presenta para optar por el grado de Doctor en Medicina por la Universidad de Málaga.

Certifica, así mismo la idoneidad de la presentación de la tesis.

Málaga, a 15 de mayo de 2016

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Málaga, a 31 de mayo de 2017

El éxito depende del esfuerzo.

Sófocles.

A mis padres, que siempre están orgullosos de nosotros.

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-Claudia, compañera de camino.

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RESUMEN EN ESPAÑOL

En este trabajo presentamos tres estudios (estudios 1, 2 y 3) con el objetivo de explorar el papel de los tratamientos mediante la repetición y la imitación junto con el tratamiento farmacológico en pacientes con afasia crónica tras accidente cerebrovascular. El primer estudio fue diseñado para tratar a tres pacientes con afasia de conducción tras lesiones en el hemisferio izquierdo. El segundo y el tercer estudio incluyeron la evaluación y el tratamiento de un paciente con afasia de conducción cruzada.

ANTECEDENTES

El lenguaje es una de las características de la especie humana - una parte importante de lo que nos hace humanos (Christiansen et al., 2003). El lenguaje es una manera de comunicarse a través de símbolos.

La afasia es la pérdida de la capacidad de producir o entender el lenguaje. Por lo general se manifiesta como una dificultad para hablar o entender el lenguaje, y la lectura y la escritura también pueden estar afectadas. Por tanto, también puede alterar al uso del lenguaje de señas y Braille. Es un trastorno del procesamiento del lenguaje que hace que el paciente esté incapacitado para la comunicación y el ajuste socio-afectivo (Berthier & Pulvermüller, 2011).

El accidente cerebrovascular es la causa más común de afasia; sin embargo, otras patologías cerebrales estructurales y ciertas afecciones neurodegenerativas (enfermedad de Alzheimer, afasia progresiva primaria) también pueden producirla. La incidencia de afasia por accidente cerebrovascular oscila entre 43-60 por 100.000 individuos en Europa y los EE.UU. La gravedad de la afasia en el período agudo después del accidente cerebrovascular es un predictor de mortalidad y dependencia. Un tercio de los pacientes con afasia después del accidente cerebrovascular son menores de 65 años de edad, y aproximadamente la mitad de ellos tendrán una esperanza de vida mayor de 5 años después del accidente cerebrovascular (Berthier & Pulvermüller, 2011). La discapacidad causada por la afasia provoca un gran impacto socioeconómico en el paciente (Pulvermüller & Berthier, 2008).

En el siglo XIX, las observaciones sobre la afasia de Broca (1865) y Wernicke (1906) sugirieron que la función del lenguaje depende de la actividad de la corteza cerebral. Al mismo tiempo, Wernicke (1906) y Lichtheim (1885) también elaboraron el primer modelo de red a gran escala del lenguaje que incorporaba vías de materia blanca de largo alcance y de corto alcance (conexiones transcorticales) en el procesamiento lingüístico. Tradicionalmente, el fascículo arcuato (AF) (ramo dorsal) se consideraba el principal camino para la repetición. La neurociencia cognitiva moderna ha proporcionado herramientas, incluida la neuroimagen, que permiten el examen in vivo de las vías de la sustancia blanca de corta y larga distancia que unen las áreas corticales esenciales para la repetición verbal. Sin embargo, se han publicado hallazgos contradictorios, con algunos investigadores defendiendo el papel de los ramos dorsal y ventral, mientras que otros sostienen que sólo participan áreas corticales (corteza parietotemporal de Silvio (Lambon & Ralph, 2014).

La afasia de conducción (CA) se refiere a un síndrome caracterizado por un habla fluida con repetición alterada, frecuentes errores parafásicos (usualmente fonémicos), pero con una comprensión relativamente preservada y una alteración en la localización y denominación de palabras (Hillis et al., 2007). El lenguaje escrito puede verse afectado de manera similar (Balasubramanian, 2005). Este síndrome generalmente ocurre en los períodos crónicos y puede observarse durante la recuperación de la afasia de Wernicke. La CA es comúnmente causada por daño en el lóbulo parietal inferior y AF (Pandey & Heilman, 2014). Ueno y Lambon Ralph (2013) demuestran que los intentos repetidos de aproximación fonética a las palabras de destino (conduite d'approche), típicamente observadas en pacientes con CA y daño dorsal-ventral dual del AF, se basa en la actividad complementaria de la corriente semántica ventral.

La recuperación de la afasia ocurre durante un período de tiempo que va desde varios meses hasta muchos años (Lee, 2010). La imitación ha jugado un papel importante en muchos tratamientos de afasia no fluente con la justificación de que la información visual complementa otra información sensorial para uso en mecanismos de habla oral (Lee, 2010).

La farmacoterapia es otro enfoque de tratamiento de la afasia que se utiliza para estimular la reorganización neural, sobre la premisa de que la recuperación funcional observada refleja directamente la reparación de los circuitos neuronales que median el lenguaje y otras funciones cognitivas (Cahana-Amitay et al., 2014). Se ha argumentado que los fármacos, como el donepezilo (DP), son particularmente prometedores para el tratamiento de la afasia en sus estadios agudos y crónicos (Berthier et al., 2011). DP es el segundo medicamento aprobado en España para la enfermedad de Alzheimer. Al igual que tacrina, mejora moderadamente la función cognitiva leve-moderada. Es un inhibidor reversible no competitivo de la acetilcolinesterasa que incrementa la concentración de acetilcolina en las sinapsis por lo que aumenta la transmisión colinérgica. Ejerce su acción de forma más selectiva a nivel cerebral, con muy poca actividad sobre las colinesterasas a nivel periférico. Al igual que otros inhibidores de la colinesterasa (tacrina), por su propio mecanismo de acción, cualquier efecto terapéutico del fármaco dependerá de la presencia de neuronas colinérgicas funcionantes. DP presenta una biodisponibilidad del 100% tras su administración oral que no se ve alterada por la presencia de alimentos. Las concentraciones plasmáticas máximas se alcanzan en 3-4 horas. Tiene un 95% de unión a proteínas plasmáticas. Se metaboliza nivel hepático por el sistema enzimático P 450 dando lugar a varios metabolitos, algunos de los cuales son activos. Tanto DP como sus metabolitos se excretan principalmente en orina y un menor porcentaje en heces. La vida media de eliminación es de 70 horas aproximadamente. El tratamiento debe iniciarse con 5 mg/día en dosis única diaria por la noche. Esta dosis debe mantenerse, por lo menos, 1 mes para permitir que se alcancen las concentraciones de estado estacionario. Tras el primer mes, la dosis puede incrementarse a 10 mg/día en dosis única. Ésta es la dosis máxima ya que dosis mayores no han sido estudiadas en ensayos clínicos. DP es un fármaco, en general, bien tolerado. Los efectos adversos más frecuentes (5-10 %) son náuseas, vómitos y diarreas. Calambres musculares, fatiga e insomnio son también otros efectos adversos detectados con menor frecuencia. La hepatotoxicidad descrita con tacrina no ha sido descrita con donepezilo. Se han descrito alteraciones psiquiátricas como alucinaciones, agitación y comportamiento agresivo que, se han resuelto cuando se ha dejado de utilizar el fármaco o se ha reducido la dosis. Aunque teóricamente podría interaccionar con medicamentos que se metabolizan a nivel hepático por las mismas isoenzimas, no se han descrito interacciones con teofilina, cimetidina o digoxina. Tampoco se han descrito interacciones con medicamentos que presentan una elevada unión a proteínas plasmáticas.

OBJETIVOS

1) Evaluar si los efectos del tratamiento con el DP combinado con dos técnicas diferentes de terapia del habla con los beneficios en déficits relacionados con la producción del habla, la comunicación cotidiana, la memoria a corto plazo y la repetición en tres pacientes con la afasia de conducción tras Lesiones del hemisferio izquierdo.

2) Describir detalladamente los déficits en la producción del habla, la comunicación cotidiana, la memoria un corto plazo y la repetición en un paciente (JAM) con AC crónica por el ictus.

3) Explorar por primera vez si JAM, un paciente con AC cruzada (afasia por daño en el hemisferio derecho), puede obtener beneficios con el entrenamiento de la repetición-imitación intensiva y tratamiento farmacológico con DP, y también si los beneficios propuestos con estas Las intervenciones pueden inducir la plasticidad estructural en la sustancia gris y los tractos de materia blanca que sustentan la producción de la comunicación y la comunicación cotidiana.

ESTUDIO 1

*Referencia: Berthier, M.L., Dávila, G., Green-Heredia, C., Moreno Torres, I., Juárez y Ruiz de Mier, R., **De-Torres, I.,** and Ruiz-Cruces, R. (2014). Massed sentence repetition training can augment and speed up recovery of speech production deficits in patients with chronic conduction aphasia receiving donepezil treatment. Aphasiology, 28, 188-218.*

La duración y la intensidad con que se debe administrar la terapia de afasia es un área importante de la investigación en curso, sin embargo hasta la fecha pocos estudios han abordado el impacto de las terapias de afasia distribuidas en el tiempo en comparación con las terapias intensivas, y los resultados disponibles son controvertidos (véase Cherney et al. , 2011, Harnish et al., 2008, Martins et al., 2013, Sage et al., 2011).

Existe un acuerdo general de que la terapia de la afasia en pacientes con accidente cerebrovascular es beneficiosa cuando se utilizan protocolos de intervención basados en la evidencia (Basso & Macis, 2011; Bhogal et al., 2003; Capple et al., 2005; Cicerone et al., 2011; , 1998). Sin embargo, todavía existen algunas limitaciones no relacionadas con las características esenciales de las intervenciones, por ejemplo, la terapia de la afasia consume mucho tiempo y es costosa (Berthier, 2005), y estas dificultades explican, entre otras razones, la brecha que existe entre lo que la investigación sobre la terapia de afasia recomienda como la cantidad apropiada de tratamiento y la provisión real (Code & Petheram, 2011). Además, la adherencia a la terapia de afasia prolongada no siempre es factible debido a problemas logísticos (por ejemplo, dificultades de transporte). Por último, la falta de voluntad para participar y el abandono de la terapia se informan comúnmente en pacientes de edad avanzada (Basso & Macis, 2011). Por lo tanto, la idea de que los beneficios proporcionados por la terapia de afasia puede ser aumentada y acelerada utilizando enfoques emergentes (por ejemplo, drogas, estimulación cerebral transcraneal y eléctrica) debe ser explorada. Por ejemplo, una terapia diferida en el tiempo no es particularmente útil en la afasia crónica, pero potenciar sus efectos beneficiosos con los fármacos se ha asociado con mejores resultados (Berthier et al., 2003, 2006). Siguiendo la misma línea de pensamiento, el siguiente paso es saber si la misma cantidad de terapia, pero administrada en un período de tiempo más corto, combinando la terapia intensiva con fármacos, puede producir mejores resultados. Curiosamente, la evidencia preliminar de un solo paciente con AC crónica demostró mayores ganancias con la terapia en masa que con terapia extendida en el tiempo, y los beneficios proporcionados por la intervención anterior se correlacionaron con el aumento de activación de los ganglios basales izquierdos y el reclutamiento en el hemisferio derecho (Harnish et al.). Por lo tanto, para obtener más conocimientos sobre la integración de terapias emergentes con intervenciones clásicas, este estudio compara la eficacia de dos diferentes intervenciones conductuales (terapia de afasia distribuida en el tiempo e intensiva) en tres pacientes con AC crónica que reciben tratamiento con el potenciador colinérgico DP.

El entrenamiento de la repetición intensiva de oraciones (MSRT) mejoró los déficit de producción de habla en pacientes con afasia de conducción crónica y lesiones perisilvianas izquierdas que recibieron tratamiento con DP.

Los efectos de MSRT se compararon con los de una terapia del lenguaje no intensiva (DSLT) en términos de producción verbal, memoria a corto plazo y repetición en pacientes con CA crónica por accidente cerebrovascular, tratados con el inhibidor de la colinesterasa DP.

Ambas intervenciones mejoraron el rendimiento en las tareas de producción de habla, pero se encontraron mayores mejoras con DP-MSRT que con DP-DSLT. El tratamiento DP-MSRT mejoró la situación basal de los pacientes, en cuanto a repetición de pares de palabras, tripletes, oraciones nuevas y experimentales con generalización de ganancias a la severidad de afasia, conexión del habla y frases de control no tratadas.

Estudios experimentales en roedores indican que la acetilcolina promueve la transmisión sináptica, estimula la plasticidad sináptica y coordina la actividad de grupos de neuronas que potencian la percepción, la atención, el aprendizaje y los procesos de memoria (Sarter et al. ., 2003, 2005). La estimulación colinérgica en condiciones experimentales facilita la neuroplasticidad, y los cambios resultantes son más evidentes cuando la modulación colinérgica se combina con el entrenamiento (plasticidad dependiente de la experiencia) (Kleim & Jones, 2008; Sarter et al., 2003, 2005). Los estudios de neuroimagen humana de los sistemas colinérgicos corroboran y extienden los relatos fisiológicos de la función colinérgica publicados en estudios experimentales en animales (véase Bentley et al., 2011).

Aunque no hemos realizado neuroimagen funcional en estos tres pacientes, nuestros resultados invitan a especulaciones sobre el papel de DP-MSRT en la modulación de las redes disfuncionales y subutilizadas. Al inicio, el desempeño deteriorado en la lista de palabras y la repetición de frases en nuestros pacientes puede atribuirse a la disminución sináptica en la vía colinérgica lateral izquierda (insula y materia blanca frontoparietal) (Buckingham & Buckingham, 2011; Gotts et al., 2002; Gotts & Plaut, 2004, McNamara & Albert, 2004, Selden et al., 1998, Tanaka et al., 2006) con compensación incompleta de los déficits por los tractos de la sustancia blanca perisilviana derecha. Sugerimos que la potenciación colinérgica con DP potenció los efectos de la terapia de afasia no sólo revirtiendo la disminución sináptica en las áreas disfuncionales del hemisferio izquierdo, sino, lo que es más importante, mediante el reclutamiento de las vías perisilvianas derechas. Recientes estudios de intervención en afasia crónica demostraron que los beneficios en la producción de habla con Terapia de Entonación Melódica (Schlaug et al., 2009; Zipse et al., 2012) y en la repetición y el nombramiento con Terapia restrictiva para la afasia (CIAT) (Breier et al., 2011) se asociaron con plasticidad funcional y estructural del AF derecho. Sugerimos que MSRT (y en menor medida DSLT) en combinación con DP también podría reclutar redes del hemisferio derecho. Después de ambos tratamientos, nuestros pacientes recuperaron la capacidad de repetir con facilidad las palabras objetivo anteriormente inaccesibles en ambas listas y frases nuevas. También recuperaron la retención del orden de las palabras como se refleja por un incremento significativo en el número de repeticiones correctas de tripletes y oraciones. Esto puede haber sido el resultado de la reversión de la disminución sináptica (Gotts & Plaut, 2002) y la reducción de activación de propagación de los competidores (Foster et al., 2012) inducida por DP. Además, es tentador argumentar que el aumento de la eficiencia neural y el mejor desempeño de las tareas promovidas por la estimulación colinérgica (Ricciardi, et. al, 2013) se reforzaron con MSRT con el objetivo de fortalecer la actividad de los tractos de la sustancia blanca perisilviana del hemisferio derecho (AF), previamente subutilizado, al servicio de la repetición. Además, la potenciación colinérgica también podría haber modulado las regiones frontoparietales implicadas en los procesos ejecutivo-atencionales (Demeter & Sarter, 2013), así como la atención y memoria a corto plazo auditivo-visual a través de una interacción dinámica entre corrientes auditivas dorsales y ventrales derechas (Majerus et al., 2012) . La recuperación de déficit de producción en pacientes con afasia fluida generalmente sigue una secuencia fija (por ejemplo, Kertesz, 1984, Kohn et al., 1996) evolucionando desde la producción inicial de neologismos relacionados con objetivos, errores y omisiones fonológicas seguidos de errores fonológicos y formales mejor identificados. Los beneficios proporcionados por las intervenciones combinadas en nuestros tres pacientes estaban en desacuerdo con el patrón habitual de recuperación de CA descrito en casos crónicos, porque tras ambas intervenciones no se vieron estos pasos aparentemente obligados de recuperación. Además, se encontró que DP-MSRT aumentó y aceleró la recuperación en comparación con DP-DCSLT.

ESTUDIO 2

Referencia: ***De-Torres, I.,*** *Dávila, G., Berthier, M.L., Walsh, S.F., Moreno-Torres, I., & Ruiz-Cruces, R. (2013). Repeating with the right hemisphere: reduced interactions between phonological and lexical-semantic systems in crossed aphasia? Frontiers in Human Neuroscience, Oct 18; 7: 675.*

Está bien establecido que la mayoría (95%) de los diestros tienen dominancia del hemisferio cerebral izquierdo para el lenguaje (Annett, 1998; Wada & Rasmussen, 2007). Una minoría (5%) de diestros tiene especialización hemisférica derecha para el lenguaje (Loring et al., 1990; Annett, 1998; Pujol et al., 1999; Knecht et al., 2002) y dominancia mixta (producción y recepción de lenguje representada en ambos hemisferios) lo que puede ocurrir tanto en cerebros sanos (Lidzba et al., 2011) como lesionados (Kurthen et al., 1992; Paparounas et al., 2002; Kamada et al., 2007; Lee et al., 2008) de individuos diestros, lo que es mucho menos frecuente.

La rareza de la lateralización completa o incompleta del lenguaje en el hemisferio derecho explica por qué sólo una minoría de individuos diestros desarrollan déficit de lenguaje después de una lesión en el hemisferio derecho (afasia cruzada) (Bramwell, 1899; Alexander et al., 1989a; Mariën et al. , 2001, 2004). Aunque la afasia cruzada es rara, el análisis del funcionamiento del lenguaje en estos sujetos representa una oportunidad ideal para examinar si su desempeño lingüístico y la arquitectura neural que sustenta las funciones lingüísticas en el hemisferio derecho son las mismas que las reportadas en sujetos con dominio del hemisferio izquierdo (Catani et al , 2007, Turken & Dronkers, 2011, y Catani & Thiebaut de Schotten, 2012). En este trabajo se reporta la aparición de afasia fluida con repeticiones severamente anormales y déficits en la comprensión de la oración (CA) en un paciente varón (JAM) que sufrió una lesión subcortical derecha severa. Esta correlación clínico-anatómica es infrecuente, pero su descripción puede iluminar aún más la organización neural del lenguaje proposicional en el hemisferio derecho. En un intento por lograr esto, en el presente estudio se delineó la localización de los daños a los tractos de sustancia blanca que sustentan la repetición del lenguaje en un paciente con la ayuda de secciones cerebrales representadas en un atlas de conexiones cerebrales humanas (Catani y Thiebaut de Schotten, 2012) y con estudio de difusión de imagen (DTI) de tractos bilaterales de materia blanca (tractografía).

La lesión que causó la afasia de JAM era de localización estriatal / capsular, abarcando el AF derecho y el fascículo frontal-occipital inferior (IFOF), el tallo temporal y la sustancia blanca debajo del giro supramarginal. Al evaluar su repetición, JAM mostró efectos de lexicalidad (repetía mejores palabras que no-palabras, pero la manipulación de otras variables léxico-semánticas ejerció menos influencia en el rendimiento de la repetición. En este paciente casi nunca se observaron los efectos de imaginabilidad y frecuencia, la producción de parafasias semánticas durante la repetición de oraciones o el mejor desempeño en la repetición de oraciones nuevas que los clichés. El estudio DTI reveló daños en el segmento derecho largo y directo del AF y el IFOF con preservación relativa de los segmentos anterior e indirecto del FA, junto con vías de la sustancia blanca perisilviana izquierda completamente desarrolladas. Utilizando el cuestionario de comunicación en las actividades de la vida diaria (CAL) se vio que la cantidad y calidad de la comunicación estaban deterioradas. Estos hallazgos sugieren (1) que las lesiones estriatales / capsulares que se extienden al AF derecho y el IFOF en algunos individuos con dominancia del lenguaje en hemisferio derecho se asocian con patrones de repetición atípicos que podrían reflejar la reducción de las interacciones entre los procesos fonológicos y léxico-semánticos; Y (2) que los pacientes con CA cruzada también pueden mostrar habilidades de comunicación reducidas a pesar de tener un habla espontánea fluida.

La afectación inferior del tronco temporal y el IFOF, superiormente al AF y la materia blanca debajo del giro supramarginal, pueden provocar limitación de acceso a la información léxico-semántica durante la repetición de listas de palabras y repetición de oraciones. La interrupción del segmento directo largo del AF derecho podría explicar el rendimiento anormal en la repetición de palabras y no palabras. La lesión del tracto ventral derecho (IFOF) que comunica la corteza insular y el putamen podría ser responsable del deterioro del proceso léxico-semántico y sintáctico necesario para la comprensión exacta de la oración y la repetición. Además, la participación de la corteza temporal basal derecha (tallo temporal, área del lenguaje basal) puede haber cortado las vías comisurales (comisura anterior) que interrumpen la conectividad funcional con su parte homóloga contralateral, limitando aún más el acceso al significado durante la comprensión (Umeoka et al., 2009; Warren et al., 2009) y también con el giro temporal posterosuperior dificultando el procesamiento fonológico (Ishitobi et al., 2000, Koubeissi et al., 2012). Es necesario un análisis más profundo de los individuos con dominancia del lenguaje del hemisferio derecho para mejorar nuestra comprensión sobre el papel de los tractos de materia blanca en la repetición del lenguaje.

ESTUDIO 3:

Referencia: ***De-Torres I.,*** *Berthier M.L., Paredes-Pacheco J., Poé-Vellvé N., Thurnhofer-Hemsi K., López-Barroso D., Torres-Prioris M.J., Alfaro F., Moreno-Torres I., Dávila G. (2017). Cholinergic potentiation and audiovisual repetition-imitation therapy improve speech production and communication deficits by inducing structural plasticity in white matter tracts. Frontiers in Human Neuroscience (in press).*

Se estudiaron cambios longitudinales cerebrales en los tractos de la materia gris y de materia blanca en JAM, varón diestro con CA crónica por una lesión subcortical derecha (afasia cruzada) tratado con dos intervenciones. Se utilizó un diseño de intervenciones múltiples en un solo paciente que incluía dos dos evaluaciones de tratamiento y dos post-tratamiento. El diseño utilizado fue un A-B-BC-D1-D2. Después del establecimiento de una línea base estable (evaluación A), el paciente recibió DP 5 (mg / día) durante 4 semanas y luego la dosis aumentó (10 mg / día) durante 12 semanas sin terapia del habla en ninguna de estas dos fases (evaluación B) . Posteriormente, el paciente continuó con DP (10 mg / día) combinado con terapia LLR (evaluación BC). Después de terminar la terapia combinada, hubo dos períodos de lavado de DP y LLR (evaluaciones D1-D2). Se evaluó ampliamente el leguaje de JAM en el momento basal (semana 0), puntos finales B (semana 16) y BC (semana 28) y en los seguimientos (semanas 36 y 44). Otros tratamientos farmacológicos (escitalopram, losartán y sitagliptina / metformina, omeprazol, baclofeno y levetiracetam) se mantuvieron sin cambios durante el ensayo. El estudio fue realizado de acuerdo con la Declaración de Helsinki y el protocolo fue aprobado por el Comité Local de Ética Comunitaria para Ensayos Clínicos y la Agencia Médica Española. Este estudio de caso único se realizó como parte de un proyecto de investigación independiente financiado por Pfizer / Eisai, España y fue diseñado, conducido y controlado por el investigador principal (MLB). El estudio se registró con el número EudraCT 2008-008481-12.

Para la planificación de la terapia logopédica específica para JAM acuñamos los principios terapéuticos de Pulvermüller y Berthier (2008):

1. Alta intensidad: alta frecuencia.

2. Relevancia para el comportamiento: práctica del lenguaje en el contexto de acciones cotidianas.

3. Focalización en la capacidad: la utilización de las capacidades preservadas del paciente, especialmente las que se utilizan para evitar la dificultad en ellas.

Agregar al criterio de larga duración, ya que la aplicamos cuatro meses de forma continuada.

JAM, en la evaluación preliminar, no presentaba dificultad en la repetición de palabras o no palabras solas, dificultad con la repetición de dos palabras y gran dificultad ante la repetición de tripletes de palabras y oraciones. La terapia planificada para él se llamó *Repite-conmigo (Look-listen&repeat*-LLR) y consiste en la repetición de listas de oraciones grabadas en vídeo. El paciente ve y escucha a una persona grabada en vídeo que dice una frase a la cámara, y, a continuación, el paciente tiene un tiempo de cinco segundos para repetir la oración. Recibe tanto la entrada fonológica como el *feedback* visual de la mímica bucal y facial. Las listas contienen 50 oraciones, salvo las primeras iniciales de iniciación y aprendizaje del método (nivel I) que son más cortas (30 oraciones). El número de palabras por frase en el nivel I es de 4,46 y en el nivel II 6,10. Trabaja un mínimo de 30 minutos por la mañana y otros tantos por la tarde durante un período de 16 semanas. Es evaluado semanalmente en la ejecución de la tarea. Se le cambia la lista de palabras semanalmente si consigue repetir correctamente el 90% de las palabras. Ninguna lista se planeó para JAM con demora para la repetición, ya que la tarea presenta suficiente grado de dificultad para él y para proporcionar un buen ritmo de exigencia semanal que vaya permitiendo mejora progresiva de los resultados. La repetición de oraciones en si misma, y no de palabras solas, por la longitud de las mismas y la necesidad de repetición en el mismo orden las palabras, supone por sí mismo un entrenamiento de la memoria a corto plazo aunque no se le pida al paciente un retraso extra antes de repetir como propone Lee (2010) en su método *IMITATE*. Todas las frases utilizadas *Repite-conmigo (LLR)* cumplen las siguientes características: palabras de alta frecuencia de uso, alta imaginabilidad y predictibilidad, longitud y dificultad gramatical creciente. Para ello utilizamos los diccionarios de frecuencia de palabras de Alameda y Cuetos (1992). Empleamos campos semánticos familiares para el paciente.

La relación causal entre los cambios plásticos observados y la modulación colinérgica es difícil de alcanzar, pero concuerda con los resultados de diferentes líneas de investigación (Mesulam et al., 1992, Raghanti et al., 2008, Bohnen et al., 2009, Hiraoka Et al., 2009, Imamura et al., 2015). El análisis postmortem del sistema colinérgico humano en el lóbulo frontal mesial (área de Brodmann 32) (Raghanti et al., 2008), uno de los orígenes anatómicos del FAT (Catani et al., 2013) y crucial para las intenciones comunicativas (Catani y Bambini, 2014), reveló densos grupos de axones colinérgicos que probablemente representan eventos locales de plasticidad o reordenamiento de circuitos (Mesulam et al., 1992; Raghanti et al., 2008). Un estudio in vivo utilizando tomografía por emisión de positrones (PET) y 1Cmetil-4-piperidinil propionato acetilcolinesterasa (AChE) en sujetos de edad media y ancianos no demenciados con afectación de la sustancia blanca periventricular de origen vascular se asoció con una menor actividad colinérgica por una interrupción en las vías colinérgicas ascendentes (Bohnen et al., 2009).

De forma complementaria, un estudio histoquímico de un paciente joven con lesiones vasculares subcorticales puras reveló ruptura de las vías ascendentes colinérgicas en la sustancia blanca profunda, aunque algunas fibras ricas en acetilcolina y neuronas corticales colinérgicas sobrevivieron incluso en las áreas de mayor denervación colinérgica (Mesulam et al., 2003). Por otra parte, el conocimiento en los sitios del cerebro donde se produce la unión de DP está proporcionando más información. Un estudio en sujetos sanos utilizando PET y [5- (11) C-metoxi]-DP mostró una concentración moderada del radiotrazador en algunas áreas corticales (giro cingulado frontal y anterior) que son los orígenes del FAT (Hiraoka et al. , 2009, Catani et al., 2013). Por último, los estudios in vitro demostraron que el tratamiento con DP, a través de la estimulación de los receptores nicotínicos, aumenta rápidamente la diferenciación oligodentrocítica y la mielinización (Imamura et al., 2015).

Las evaluaciones con neuroimagen, DTI y morfometría basada en voxel (VBM) se realizaron basalmente y tras los dos periodos de tratamiento. Se comparó con la neuroimagen de 21 controles sanos varones adultos. El tratamiento con DP de forma aislada y combinado con LLR indujo una marcada mejoría en la afasia y los déficits de comunicación, así como en medidas seleccionadas de producción de habla conectada y repetición verbal. Las ganancias obtenidas en la producción de habla se mantuvieron muy por encima de las puntuaciones iniciales incluso cuatro meses después de terminar la terapia combinada. El DTI longitudinal mostró plasticidad estructural en el tracto Aslant frontal derecho (FAT) y segmento directo del AF (DSAF) con ambas intervenciones. No se encontraron cambios estructurales favorables en otros tramos de materia blanca ni en áreas corticales unidas por estos tractos. En conclusión, la potenciación colinérgica sola y combinada con una terapia de afasia basada en modelos mejoró los déficits de lenguaje promoviendo cambios estructurales plásticos en los tractos de la sustancia blanca derecha.

Numerosos estudios demuestran la eficacia de la terapia logopédica intensiva de la afasia, pero ello conlleva limitaciones económicas si se precisa de un terapeuta presencial en todas las horas de tratamiento. Existen alternativas factibles como entrenar a un familiar / cuidador en la facilitación de la terapia al paciente, o el uso de programas informáticos. Otra ventaja de estas opciones supone la posibilidad de tratamiento en los ambientes habituales del paciente y se minimizan dificultades como el desplazamiento al lugar de la terapia o la incompatibilidad de horarios (Pulvermüller & Berthier, 2008). La telerehabilitación consiste en la aplicación de las Tecnologías de la Información y la Comunicación a la prestación de servicios de rehabilitación a distancia. Un ejemplo puede ser la utilización de videos interactivos en el domicilio del paciente para llevar a cabo el entrenamiento logopédico, como hemos aplicado en el caso objeto de este trabajo. Farreny et al., (2012) defienden que los ordenadores han sido integrados a prácticamente todas las áreas de la actividad humana. Permiten una presentación, organización y control sistemático de la información, y en consecuencia, pueden ser una herramienta de gran utilidad en la terapia del lenguaje. El aumento de la demanda de programas de rehabilitación en la mayoría de países de nuestro entorno se debe tanto al incremento de la longevidad de la población, como al creciente número de individuos que presentan algún grado de discapacidad como resultado de múltiples procesos patológicos. El diseño de los diferentes programas de rehabilitación debe superar con frecuencia barreras geográficas o económicas que dificultan su implantación y limitan su eficacia. La telerehabilitación se presenta como una alternativa útil y accesible desde el punto de vista tecnológico y económico (Farreny et al., 2012).

CONCLUSIONES

1) En el estudio 1 se demuestra, por primera vez, que el tratamiento combinado el entrenamiento intensivo de repetición de oraciones (MSRT) (40 horas en ocho semanas) con DP asocia mejores resultados en los déficits de producción de habla que los Que se obtuvo con el tratamiento combinado de DP y terapia del habla menos intensiva (DSLT) (40 horas en 16 semanas). Aunque ambos tipos de intervenciones fueron eficaces para mejorar los déficits de producción de

habla, MSRT combinado con DP aumentó y aceleró los beneficios proporcionados por la terapia más extendida en el tiempo (DSLT). Estos hallazgos demuestran que los tratamientos intensivos están asociados con los mejores resultados que las terapias tradicionales, no intensivas. Además, estos hallazgos sugieren que la combinación de un tratamiento biológico (DP) con las intervenciones basadas en los modelos de son estrategias prometedoras para el tratamiento de la post-ictus.

2) Para implementar una intervención terapéutica similar a la del Estudio 1, se evaluó un paciente (JAM) con la afasia de conducción crónica post-ictus con el objetivo de establecer una evaluación basal completa (Estudio 2). Encontramos deficiencias de lenguaje y comunicación estabilizadas. Los déficits de lenguaje afectaron principalmente a la repetición y el perfil de estos déficits atípicos, lo que refleja una menor interacción entre los sistemas semánticos, fonológicos y léxicos. Este hallazgo sugiere que la interacción entre ambos hemisferios cerebrales en pacientes con afasia cruzada es atípica.

3) La intervención basada en modelos utilizando un fármaco (DP) y la terapia de imitación repetitiva con apoyo audiovisual en el paciente JAM mejoró los déficits de lenguaje y comunicación (Estudio 3). Estos cambios positivos fueron apoyados por cambios plásticos altamente focales en los tractos de la sustancia blanca derecha (FAT y segmento directo del AF derecho). No encontramos plasticidad estructural en el área de materia gris interconectada por estos tractos ni en el hemisferio izquierdo.

PREFACE

The aims of these 3 studies (Studies 1, 2 and 3) was to explore the role of repetition and imitation training and drug treatment in patients with chronic post-stroke conduction aphasia (CA). The first intervention study was designed to treat three patients with CA after lesions in the left hemisphere. The second and third studies involved the evaluation and treatment of a patient with crossed CA. The abstracts of these three studies are presented separately at the beginning of each study.

Prólogo

Los objetivos de estos 3 estudios (estudios 1, 2 y 3) son explorar el papel de tratamientos a través de la repetición y la imitación, junto con tratamiento farmacológico en pacientes con afasia crónica tras accidente cerebrovascular). El primer estudio fue diseñado para tratar a tres pacientes con afasia de conducción tras lesiones en el hemisferio izquierdo. El segundo y el tercer estudio incluyeron la evaluación y el tratamiento de un paciente con afasia de conducción cruzada. Los resúmenes de estos tres estudios se presentan por separado al comienzo de cada uno, como se podrá leer a continuación.

ABBREVIATIONS

AF: Arcuate fasciculus

ASAF: Anterior segment of the AF

AVSTM: Auditory-verbal short-term memory

CA: Conduction aphasia

CAL: Communicative activity log

CIAT: Constraint-induced aphasia therapy

CIU: Correct information unit

DP: Donepezil

DSAF: Direct segment of arcuate fasciculus

DSLT: Distributed speech-language therapy

DTI: Diffusion tensor imaging

FAT: Frontal aslant tract

IFOF: Inferior frontal-occipital fasciculus

LLR: Look-listen and repeat

MIT: Melodic intonation therapy

MSRT: Massed sentence repetition therapy

PALPA: Psycholinguistic assessments of language processing in aphasia

rsfMRI: Resting state functional magnetic resonance imaging

SLF: Superior longitudinal fasciculus

SMA: Supplementary motor area

VBM: Voxel-based morphometry

WAB: Western aphasia battery

INTRODUCTION

Language is one of the hallmarks of the human species – an important part of what makes us human (Christiansen et al., 2003). Language is a way to communicate through symbols. Aphasia is the loss of ability to produce and/or understand language. This usually manifests as a difficulty speaking or understanding spoken language and reading and writing are also usually impacted. Aphasia can also affect the use of sign language and Braille. Aphasia is a disorder of language processing that makes the patient disabled for communication and social-affective adjustment (Berthier & Pulvermüller, 2011). The negative impact of aphasia can be magnified in anxiety-provoking environmental circumstances such as new situations, noisy environments, distracting elements, or several people speaking at the same time.

Stroke is the most common cause of aphasia; however any structural brain pathology and certain neurodegenerative conditions (Alzheimer’s disease, primary progressive aphasia) can produce aphasia as well. The incidence of aphasia after stroke ranges from 43-60 per 100,000 individuals in Europe and U.S. The severity of aphasia in the acute period after stroke is a predictor of mortality and dependence. A third of patients with aphasia after stroke are under 65 years of age, and approximately half of them will have a life expectancy greater than 5 years after stroke (Berthier & Pulvermüller, 2011). The disability caused by aphasia provokes a great social-economical impact to the patient (Pulvermüller & Berthier, 2008).

In the nineteenth century, ground-breaking observations on aphasia by Broca (1865) and Wernicke (1906) suggested that language function depends on the activity of the cerebral cortex. At the same time, Wernicke (1906) and Lichtheim (1885) also elaborated the first large-scale network model of language which incorporated long-range and short-range (transcortical connections) white matter pathways in language processing. The arcuate fasciculus (AF) (dorsal stream) was traditionally viewed as the major language pathway for repetition, but scientists also envisioned that white matter tracts traveling through the insular cortex (ventral stream) and transcortical connections may take part in language processing. Modern cognitive neuroscience has provided tools, including neuroimaging, which allow the in vivo examination of short- and long-distance white matter pathways binding cortical areas essential for verbal repetition. However, this state of the art on the neural correlates of language repetition has revealed contradictory findings, with some researchers defending the role of the dorsal and ventral streams, whereas others argue that only cortical hubs (Sylvian parieto-temporal cortex) are crucially relevant (Berthier & Lambon Ralph, 2014).

Conduction aphasia

CA refers to a syndrome characterized by fluent speech with impaired repetition, frequent paraphasic errors (usually phonemic) but relatively preserved comprehension and impaired word finding and naming (Hillis et al., 2007). Written language may be similarly affected (Balasubramanian, 2005). This syndrome usually occurs in the chronic periods and it may be observed during recovery from a Wernicke aphasia.

CA is commonly caused by damage to the inferior parietal lobe and AF (Pandey & Heilman, 2014). In a computational modeling investigation of the dual dorsal-ventral pathway implicated in verbal repetition, Ueno and Lambon Ralph (2013) demonstrate that the successful phonetic approximations to target words (conduite d'approche), typically observed in patients with CA and damage to the dorsal pathway (AF), relies on the complementary activity of the ventral semantic stream.

Speech and Language Therapy

Recovery from aphasia occurs over a period of time ranging from several months to many years (Lee, 2010). Imitation has played an important role in many treatments for non-fluent aphasia with the rationale that visual input complements other sensory information for use in oral speech mechanisms (Lee, 2010).

Pharmacotherapy of Aphasia

Pharmacotherapy is one of several biological approaches for the treatment of aphasia which is used to stimulate neural reorganization, on the premise that observed functional recovery directly reflects reparation of neural circuits mediating language and other cognitive functions (Cahana-Amitay et al., 2014). Drugs, such as donepezil (DP) have been argued to be particularly promising for aphasia treatment in its acute and chronic stages (Berthier et al., 2011).

OBJECTIVES

1) To evaluate whether the effects of treatment with the cholinesterase inhibitor donepezil (DP) combined with two different speech therapy techniques provide benefits in deficits involving speech production, everyday communication, short-term memory, and repetition in three patients with chronic post-stroke CA after left hemisphere lesions.

2) To describe the profile deficits in speech production, everyday communication, short-term memory, and repetition in a patient (JAM) with chronic post-stroke crossed CA.

3) To address for the first time the question of whether JAM, a patient with crossed CA (e.g., aphasia after right hemisphere damage), can obtain benefits with intensive repetition-imitation training and pharmacological treatment using donepezil, and also if the hypothetized benefits with these interventions can induce structural plasticity in grey matter and white matter tracts underpinning speech production and everyday communication.

Objetivos

1) Evaluar si los efectos del tratamiento con donepezilo combinado con dos técnicas diferentes de terapia del habla proporcionan beneficios en déficits relacionados con la producción del habla, la comunicación cotidiana, la memoria a corto plazo y la repetición en tres pacientes con afasia de conducción tras lesiones del hemisferio izquierdo.

2) Describir detalladamente los déficits en la producción del habla, la comunicación cotidiana, la memoria a corto plazo y la repetición en un paciente (JAM) con AC crónica por ictus.

3) Explorar por primera vez si JAM, un paciente con AC cruzada (afasia por daño en el hemisferio derecho), puede obtener beneficios con el entrenamiento de la repetición-imitación intensiva y tratamiento farmacológico con donepezilo, y también si los beneficios propuestos con estas intervenciones pueden inducir la plasticidad estructural en la sustancia gris y los tractos de materia blanca que sustentan la producción del habla y la comunicación cotidiana.

STUDY 1: Distributed and massed sentence repetition training improved speech production deficits in patients with chronic conduction aphasia and left perisylvian lesions receiving donepezil treatment.

Reference: Berthier, M.L., Dávila, G., Green-Heredia, C., Moreno Torres, I., Juárez y Ruiz de Mier, R., ***De-Torres, I.,*** *and Ruiz-Cruces, R. (2014). Massed sentence repetition training can augment and speed up recovery of speech production deficits in patients with chronic conduction aphasia receiving donepezil treatment. Aphasiology, 28, 188-218.*

Abstract - Study 1

The effects of massed sentence repetition therapy (MSRT) were compared to those of distributed speech-language therapy (DSLT) in measures of verbal output, short-term memory and repetition in patients with chronic post-stroke CA receiving treatment with the cholinesterase inhibitor donepezil (DP). Both interventions improved performance in speech production tasks, but better improvements were found with DP-MSRT than with DP-DSLT. Larger treatment effects were found for DP-MSRT in comparison with baselines and DP-DSLT in repetition of word pairs and triplets, and novel and experimental sentences with generalisation of gains to aphasia severity, connected speech and non-treated control sentences. In conclusion, combined interventions with DP and two different aphasia therapies (DSLT and MSRT) significantly improved speech production deficits in CA, but DP-MSRT augmented and speeded up most benefits provided by DP-DSLT.

Introduction- Study 1

Conduction aphasia (CA) is characterised by a disproportionate deficit in repetition in the context of fluent verbal output and relative sparing of auditory comprehension (Albert, Goodglass, Helm, Rubens, & Alexander, 1981; Berthier, Dávila, García-Casares, & Moreno-Torres, 2014; Kohn, 1992). However, in recent years, CA has been fractionated in a spectrum of syndromes which are to some extent dependent on aphasia severity, moment of aphasia evaluation, type of repetition tasks used, lesion location and availability of compensatory brain mechanisms (Berthier et al., 2012; Gvion & Friedmann, 2012; Nadeau, 2001). Within this syndromic spectrum, two major types of CA (reproduction and repetition) prevail (Shallice & Warrington, 1977). The reproduction subtype is characterised by phonemic paraphasias in all verbal modalities and recurring production of sequential phonemic approximations to the target word aimed to self-repair errors (conduite d'approche), a pattern of deficits variously ascribed to deficits in speech programming (Bernal & Ardila, 2009), output phonological encoding (Kohn, 1992) or combined deficits in sensory- motor integration and phonological short-term memory (Buchsbaum et al., 2011; Hickok, Houde, & Rong, 2011). The repetition subtype is less severe than the previous one because it shows virtually isolated repetition deficits which have been linked to a selective impairment in auditory-verbal short-term memory (AVSTM) (Shallice & Warrington, 1977).

Acute post-stroke CA roughly accounts for 13% of all aphasic syndromes, with most patients achieving good recovery, yet this figure increases (~23%) when chronic aphasic patients are taken into account (Laska et al., 2001) because CA often represents the end-stage of more severe aphasic syndromes (e.g., global aphasia, Wernicke’s aphasia) (Kertesz, 1984). In chronic CA, residual phonological errors and self-corrections may hinder verbal output and functional communication, and deficits in AVSTM additionally disrupt comprehension of complex sentences. Moreover, even in patients who attain good outcomes, the profile of CA may latently remain post recovery (Ueno et al., 2011), particularly when patients are subjected to demanding testing conditions (Berthier et al., 2012; Jefferies et al., 2006). Collectively, these findings imply that devising neuroscience-driven interventions for residual CA could be an important area of enquiry. However, despite its prevalence, reports dealing with theoretically motivated treatments for CA are scant. In the next section, we describe interventions aimed to improve speech production and AVSTM in CA.

In 1833, the Dublin physician Jonathan Osborne (1794–1864) examined repeatedly over the course of a year a young aphasic patient with fluent polyglot jargon, good comprehension of spoken and written words and poor repetition (Breathnach, 2011), a combination of features which Wernicke comprehensively described more than 40 years later under the rubric of CA (De Bleser et al., 1993; Weiller et al., 2011; Wernicke, 1906, 1977). After the initial evaluation, Osborne recommended his patient “to commence learning to speak like a child repeating first, the letters of the alphabet, and subsequently words, after another person” (Breathnach, 2011, p. 25). In a follow-up evaluation eight months later, repetition exercises lead to considerable improvements in spontaneous speech and repetition. The beneficial effects of this intervention were overlooked until recently (see below) perhaps because therapies training the most affected language domain (repetition) to improve fluency and content in spontaneous speech were viewed counter- productive. In this context, in a tutorial textbook of acquired aphasia, Taylor Sarno contended “The therapist chooses those techniques or exercises that allow the patient to use preserved skills, thereby increasing the chances for successful performance” (Taylor Sarno, 1998, p. 617). Although Taylor Sarno’s recommendation was accepted as a dogma by many speech therapists, recent developments challenge this classical thinking and modern rehabilitation strategies reveal that interventions directed to repair damaged processes are effective (Basso, 2003). For example, Basso suggests that an “Intervention should be targeted to the underlying damaged processes rather than simply treating the presenting symptoms or looking for a strategy that bypasses the deficit” (Basso, 2003, p. 199). Interventions aimed to remediate language deficits in CA have been reported applying traditional techniques (Cubelli et al., 1988; Léger et al., 2002) or modern massed therapies such us Constraint-Induced Aphasia Therapy (CIAT) (Harnish, et al., 2008; Pulvermüller et al., 2001). Since some interventions in CA tailored to improve speech production also trained other language domains (reading aloud, picture naming) besides repetition (Cubelli et al., 1988; Léger et al., 2002), these studies are not reviewed here.

In the past two decades, several single-case studies used repetition exercises to improve speech production and AVSTM in CA. Kohn, Smith and Arsenaut (1990) were the first researchers that used sentence repetition exercises in a patient with a moderately severe chronic reproduction CA who had greater speech fluency in repetition than in conversation. The authors selected repetition as the training strategy because they wanted to increase speech fluency rather than accuracy in word production. Two sets of 20 sentences were constructed. One set included sentences rich in semantic content and was composed of substantives and verbs (e.g., “She was there”), whereas the other set was composed of sentences containing pronouns, adverbs and functor verbs (e.g., “Tom played ball”). After two months of sentence repetition exercises carried out at home with the help of family members, improvements were documented in sentence repetition with generalisation of benefits to picture description. The authors concluded that benefits provided by repetition exercises resulted from improvement in phonemic planning in all output modalities rather than from gains in AVSTM (Kohn et al., 1990).

Francis, Clark, and Humphreys (2003) trained word and sentence repetition to improve sentence comprehension in a patient with mild receptive aphasia associated to recurrent strokes. Gains after treatment were observed in digit span, long-term word recognition memory, sentence repetition and Token Test. However, since the patient had suffered recurrent stroke episodes, it has been argued that spontaneous improvement may have played a role in the recovery process (Salis, 2012).

Majerus, Van der Kaa, Renard, Van der Linden, and Poncelet (2005) treated a patient with a phonological short-term memory disorder in two phases. In the initial phase, the patient was asked to repeat pairs of bi-syllabic words or non-words immediately after hearing the stimuli. When the patient achieved a stabilisation in phonological production, delayed repetition tasks (repetition after a 5-second filled interval) that required holding meaningful and meaningless phonological information in AVSTM were used. The patient was treated during 16 months (twice per week) and modest improvements were found in digit and non-word span, non-word repetition and rhyme judgements. Also, the patient had the personal impression of better comprehension in conversational contexts involving more than two partners.

Koenig-Bruhin and Studer-Eichenberger (2007) treated a stroke patient with chronic repetition CA. The purpose was to examine whether deficits of the temporary storage of verbal information could be improved with sentence repetition exercises. Therefore, they trained repetition of sentences that were of four to seven words long with increasing delays between the stimulus and response. The control task consisted of repeating words of four to six words without delay. Treatment significantly improved sentence repetition, and gains were generalised to sentence length in oral production and spans for digits and bi-syllabic words. These findings were interpreted in the frame of the interactive spreading activation model of speech processing as reflecting a slowing down in activation decay (Koening-Bruhin & Studer- Eichenberger, 2007).

In a comprehensive study, Kalinyak-Fliszar, Kohen, and Martin (2011) trained repetition to improve AVSTM and executive processing in a patient with chronic CA using a multiple-baseline, multiple-probe design across behaviours. These researchers used repetition of words and non-words in immediate and delayed conditions. Gains in repetition performance were mostly restricted to treated items, but post-treatment measures of language ability indicated improvements in single and multiple word-processing tasks, verbal working memory tasks and verbal span. Taken together, these results suggest that treating these deficits directly with repetition training may improve speech production (repetition), AVSTM and executive-attentional processes, presumably by reinforcing activation and maintenance of linguistic information in AVSTM (Kalinyak-Fliszar et al., 2011; Koening-Bruhin & Studer-Eichenberger, 2007).

WHY TRAINING REPETITION IN CONDUCTION APHASIA HELPS?

The abovementioned strategy of training repetition to improve speech production and AVSTM deficits is based on scientific knowledge gathered from lesion studies (Gold & Kertesz, 2001; Kohn et al., 1990; Martin et al., 1994; Schlaug et al., 2009; Zipse et al., 2012) and computational network modelling (Dell et al., 2007). Collectively, results from these studies suggest that the functional mechanisms suitable of reparation in CA are a variable combination of pathological reduction of network connection strength, rapid decay of activation in semantic-lexical-phonological networks and restricted AVSTM (Gold & Kertesz, 2001; Jefferies et al., 2007; Kalinyak-Fliszar et al., 2011; Koening-Bruhin & Studer-Eichenberger, 2007; Martin, 1996; Martin & Saffran, 2002). Failure of these mechanisms can be inferred even in patients with mild CA who, in spite of being able to repeat single words with ease (Caplan & Waters, 1992), show abnormal repetition performance when task demands are increased (repetition of word lists and sentences, delayed repetition) (Jefferies et al., 2007). It has been contended that auditory repetition under stressing conditions may adversely impact performance because connection strength and maintenance of language traces in dysfunctional areas of the left hemisphere are unstable (Martin et al., 1994; Martin & Saffran, 2002) with little room for natural compensation by contralateral homotopic regions (see data from patient JVA in Berthier et al., 2012). In support, knowledge from both computational network modelling (Ueno et al. 2011) and resting state functional magnetic resonance imaging (rsfMRI) in patients with focal brain lesions to critical areas (e.g., connectors) (Gratton et al., 2012) shows that disruption of network architecture impacts in nearby and remote components of the networks and even in contralesional areas. In chronic CA patients with extensive left hemisphere lesions, these remote effects may result in reduced function and failure to successfully recruit alternative neural systems (e.g., right perisylvian white matter pathways). Therefore, implementing massed and highly focused therapies, like sentence repetition training, might be useful to facilitate the use of alternatives routes when the original ones are enduringly damaged. Massed sentence repetition therapy aims, as other neuroscience-inspired therapies (CIAT) (Pulvermüller et al., 2001), the potentiation of both associationist (or coincident) Hebbian learning (Hebb, 1949) and interconnectivity of language with other processes (attention, executive function, motor system) as well as the attenuation of the deleterious effect of learned non-use in the persistence of cognitive deficits after brain injury (see Pulvermüller & Berthier, 2008).

The neural mechanisms promoting recovery from speech production deficits in response to sentence repetition/imitation training have been examined in patients with non-fluent Broca's aphasia and improvements were related to recruitment of left ventral stream (inferior fronto-occipital fasciculus [IFOF]) when this white matter bundle was spared by the lesion (Fridriksson et al., 2012) or right hemisphere networks in cases with large left hemisphere lesions (Schlaug et al., 2009; Zipse et al., 2012). A complimentary participation of the mirror neuron system (Ertelt & Binkofski, 2012; Small et al., 2010) or visual areas (Fridriksson et al., 2012) has been suggested as well. However, at present, the biological roots of recovery from CA have not been investigated, yet the beneficial role of repetition training can be tentatively inferred from the abovementioned data (Zipse et al., 2012). Before addressing this topic, we will briefly outline the current state-of-the-art of the neural mechanisms underpinning normal language repetition and maintenance of the verbal trace in short-term memory. This would allow the elaboration of a conceptual framework for understanding the neural mechanisms instantiating residual repetition in CA and the development of rehabilitation strategies for exploiting this residual capacity to facilitate recovery.

The role of cortical areas (inferior parietal lobule, superior temporal gyrus) and white matter pathways (AF, IFOF) underpinning repetition is still a matter of controversy (Bernal & Ardila, 2009; Berthier et al., 2012; Dick & Tremblay, 2012; Saur et al., 2008). Some authors defend the role of cortical areas (e.g., Bernal & Ardila, 2009), whereas others maintain that perisylvian white matter tracts (AF, IFOF) are the anatomic signatures of repetition (Berthier et al., 2012; Friederici & Gierhan, 2013; Geschwind, 1965; Gierhan, 2013; Rijntjes, et al., 2012; Saur et al., 2008). Diffusion tensor imaging (DTI) studies have examined the anatomy and connectivity of white matter tracts subserving repetition (Catani et al., 2005; Catani & Thiebaut de Schotten, 2012; Catani et al., 2007; Saur et al., 2008). DTI studies not only allow delineation of the fine architecture of long-distance and short-distance white matter tracts (for review see Geva, et al., 2011), but can also reveal anatomic asymmetries which might be related to differences in repetition performance in normal and brain- damaged subjects (Berthier et al., in press; Catani et al., 2007). Long-distance white matter tracts binding remote cortical language sites are segregated in a dual stream architecture (dorsal and ventral streams), wherein the role of the dorsal auditory stream system (AF, superior longitudinal fasciculus) is to monitor auditory-motor integration of speech by allowing a fast and automated preparation of copies of the perceived speech input (Peschke et al., 2009; Rijntjes et al., 2012; Saur et al., 2008). The ventral auditory stream (IFOF, extreme capsulae and uncinate fasciculus) participates in the mapping of sounds onto meaning (Cloutman, 2012; Peschke et al., 2009; Saur et al., 2008) although the precise functional role of every tract is still controversial (Duffau et al., 2009; Harvey et al., 2013). Word and sentence information temporarily activated in the dorsal and ventral language processing networks is presumably controlled and maintained via a left fronto-parietal attention processing network (Majerus, 2013; Majerus et al., 2012).

Anatomically, the dorsal stream (AF) is more lateralised to the left hemisphere than other white matter tracts including the ventral stream (IFOF) (Hickok & Poeppel, 2007; Nucifora et al., 2005) and the former also has individual differences in its intra- and inter-hemispheric architecture (Catani & Thiebaut de Schotten, 2012; Catani et al., 2007). The most common anatomical pattern of the AF is characterised by extreme leftward lateralisation of the direct segment and lack of this segment in the right hemisphere, a configuration that predominates in males. A second pattern has been identified having a less strongly lateralised long direct segment in the left hemisphere than the previous pattern and it is associated with a vestigial right hemisphere direct component. The third pattern, usually documented in females, has a roughly symmetrical distribution of direct segments (Catani & Mesulam, 2008). Data from healthy subjects revealed that the auditory-motor integration needed to learn new words depends on the activity of the left AF (López-Barroso et al., 2013) and also that superior verbal learning through repetition correlates with the symmetrical pattern (Catani et al., 2007). The advantage for certain cognitive functions (verbal learning) amongst individuals having symmetrical AF raises the possibility that left brain-damaged patients praised with a well-developed direct segment of the right AF may be ideal candidates to rehabilitation strategies tailored to exploit repetition through this pathway (Schlaug et al., 2009; Zipse et al., 2012). In this context, DTI performed before and after Melodic Intonation Therapy (MIT) (Sparks et al.,1974) and CIAT (Pulvermüller & Berthier, 2008; Pulvermüller et al., 2001) in patients with Broca's aphasia showed that post-therapy gains in language performance correlated with structural plasticity of the right AF (Breier et al., 2011; Schlaug et al., 2009; Zipse et al., 2012).

Verbal repetition entails the imitation of not only incoming auditory stimuli, but also visual signals through action observation (Iacoboni et al., 1999; Keysers et al., 2003; Kohler et al., 2002). Imitation, action understanding, learning and language may depend partially on the activity of the mirror neuron system. The mirror neurons are located in Brodmann's area 44, superior temporal gyrus and inferior parietal lobule. Since these cortical areas are interconnected through the auditory dorsal stream (AF), it has been contended that the mirror neuron system and the dorsal white matter bundle are tightly intertwined (Arbib, 2010; Corballis, 2010). This would imply that interventions combining repetition of auditory signals with visual stimuli (viewing the mouth of a person speaking aloud the to-be-repeated material) would create a more compelling scenario for rehabilitation than repeating auditory stimuli alone. Fridriksson and colleagues (Fridriksson et al., 2012) found that audiovisual feedback improved more spontaneous speech than audio-only feedback in patients with chronic Broca's aphasia. A similar line of thought has been exploited to devise a new intervention (IMITATE) to train repetition and imitation of audio- visual stimuli in aphasic patients (Lee et al., 2010; Small et al., 2010). Up to now, IMITATE has not been used to treat CA patients, but based on the abovementioned role of repetition training in previous cases, it is tempting to envision that this technique would also apply for CA patients. Despite the improvements provided by auditory repetition training in spontaneous speech (Kohn et al., 1990), sentence comprehension (Francis et al., 2003) and AVSTM (Kalinyak-Fliszar et al., 2011), it can be wondered whether complementary interventions in CA may enhance recovery further. One potential strategy, which is discussed below, is strengthening language gains provided by aphasia therapy with pharmacotherapy.

CAN CHOLINERGIC MODULATION BOOSTS APHASIA THERAPY EFFECTS IN CONDUCTION APHASIA?

The efficacy of aphasia therapy is well proven (Basso, 2003; Cherney, 2012; Varley, 2011). Nonetheless, developing complementary strategies to augment and speed up its benefits is advantageous (Allen et al., 2012; Berthier & Pulvermüller, 2011; Small & Llano, 2009). Amongst these strategies, drug therapy is emerging as a promissory option to augment cognitive function in both healthy individuals (Husain & Mehta, 2011) and brain-damaged patients (Berthier et al., 2011; Shisler et al., 2000; Small & Llano, 2009). The basic idea behind using drugs to treat aphasia is that focal brain lesions interrupt the ascending projections of major neurotransmitter systems (e.g., acetylcholine, dopamine) from basal forebrain or brainstem to cerebral cortex and subcortical nuclei causing synaptic depression in both perilesional areas and remote regions (Berthier & Pulvermüller, 2011; Gotts & Plaut, 2002). Thus, drugs enhancing or leveraging the activity of neurotransmitters in dysfunctional but still viable speech and language areas can improve aphasic deficits. Moreover, since executive functions and attention resources may be abnormal in patients with CA (Kalinyak-Fliszar et al., 2011), restoring neurotransmitter activity in non-eloquent areas mediating these functions with drugs (DP) that modulate these cognitive functions

(Sarter et al., 2003; Sarter et al., 2005) may contribute to augment the gains obtained with repetition therapy. In the same vein, improving cholinergic activity in other non-language regions (e.g., cingulate gyrus, orbitofrontal cortex, basal ganglia) can likewise contribute to indirectly boost language functions by improving functional communication, cognitive control, goal-directed behaviour and mood (Berthier, 2012; Whyte et al., 2008).

Cholinergic agents are commonly used to treat Alzheimer's disease (Birks, 2006). On the basis of their beneficial effects on language deficits and repetitive verbalisation (statements, stories) in patients with Alzheimer's disease (Asp et al., 2006; Rockwood et al., 2007) and cognitive deficits of vascular origin (Barrett et al., 2011), the use of cholinergic drugs (DP and galantamine) have been extended to treat post-stroke aphasia. Drugs targeting the cholinergic system were used for the first time to treat aphasic deficits in the late 1960s (Luria et al., 1969), and these agents recently led to evidence for beneficial effects on naming and other language functions in post-stroke aphasia (Berthier et al., 2006; Berthier et al., 2003; Chen et al., 2010; Hong et al., 2012; Tanaka et al., 2006). Anatomical studies in the human brain reveal that the perisylvian language cortex is innervated by cholinergic fibres emanating from the nucleus basalis of Meynert or Ch4 group (Boban et al., 2006; Mesulam, 2004; Simić et al., 1999) and also that cholinergic activity is greater in the left temporal lobe than in the right one (Klein & Albert, 2004). Basal forebrain cholinergic projections are not only directed to the cortical language core as they also innervate more discrete cortical fields (e.g., cingulate gyrus, precuneus, orbitofrontal cortex) and cholinergic projections arising from the upper brainstem modulate the activity of thalamus and basal ganglia (Mesulam et al., 1992).

The modulation of the cholinergic system in post-stroke aphasia seems to be beneficial even when unpaired with aphasia therapy (Chen et al., 2010; Hong et al., 2012). Nevertheless, in light of the growing experimental data showing that cortical map plasticity induced by cholinergic agents can be enhanced further as soon as the cholinergic stimulation is administered in combination with behavioural training (Ramanathan et al., 2009), recent intervention trials in aphasia successfully combined cholinergic stimulation with aphasia therapy (Berthier et al., 2003, 2006). The mechanisms by which cholinergic stimulation promote recovery from aphasia are still unknown, but several mechanisms has been proposed to explain how cholinergic modulation facilitates access to target words during behavioural training including reversion of synaptic depression (Gotts & Plaut, 2002), reduction of spreading activation of competitors (Foster et al., 2012) and increase of speed and accuracy of information processing (Berthier & Green, 2007). In other words, it is possible that cholinergic modulation makes brain structure a more fertile ground for behavioural intervention.

THE PRESENT STUDY

The duration and intensity with which aphasia therapy need to be administered is an important area of ongoing research, yet to date few studies have addressed the impact of distributed as compared to massed aphasia therapies on outcomes and available results are controversial (see Cherney et al., 2011; Harnish et al., 2008; Martins et al., 2013; Sage et al., 2011). There is general agreement that aphasia therapy in stroke patients is beneficial when evidence-based protocols of intervention are used (Basso & Macis, 2011; Bhogal et al., 2003; Cappa et al., 2005; Cicerone et al., 2011; Robey, 1998). However, some limitations not related to the essential characteristics of the interventions still exist. To name a few, aphasia therapy is time consuming and expensive (Berthier, 2005), and these difficulties would explain, amongst other reasons, the gap that exists between what the research on aphasia therapy recommends as the appropriate amount of treatment and the actual provision in several countries (Code & Petheram, 2011). Moreover, adherence to prolonged aphasia therapy is not always feasible due to logistic problems (e.g., transportation difficulties). Finally, unwillingness to participate and abandonment of therapy are commonly reported in elderly patients (Basso & Macis, 2011). Therefore, the idea that the benefits provided by aphasia therapy can be augmented and speeded up using emerging approaches (e.g., drugs, transcranial and electrical brain stimulation) needs to be explored. For example, DSLT is not particularly useful in chronic aphasia, but potentiating its beneficial effects with drugs has been associated with better outcomes (Berthier et al., 2003, 2006). Following the same line of thought, the next step is to know if the same amount of therapy but administered in a shorter period of time combining massed, theoretically motivated interventions with drugs may yield better outcomes. Interestingly enough, preliminary evidence from a single patient with chronic CA demonstrated greater gains with massed therapy than with distributed therapy, and benefits provided by the former intervention correlated with increased left basal ganglia and right hemisphere recruitment (Harnish et al., 2008). Therefore, to gain further knowledge on the integration of emerging therapies with classical interventions, this study compares the efficacy of two different behavioural interventions (distributed and massed aphasia therapies) in three patients with chronic CA receiving drug treatment with the cholinergic enhancer DP.

Methods- Study 1

PARTICIPANTS

The three male patients who participated in the present study had been included in a 20-week open-label pilot trial evaluating the effects of DP and DSLT in chronic post- stroke aphasia (total sample = 11 patients) (Berthier et al., 2003). Eligible partici- pants for that trial had to meet the following criteria: (1) native speaker of Spanish, (2) right handed, (3) between the ages of 18 and 70 years, (4) chronic aphasia (> 1 year) and (5) left hemisphere stroke lesion. After the last end point of the trial (washout phase, week 20), these three patients were invited to take part in an extension phase (8 weeks) combining DP with MSRT. All three patients were selected because they had relatively homogeneous language deficits of lesser severity (baseline WAB-AQ score: [mean ± SD] 72.4 ± 9.6) than the other eight patients (baseline WAB-AQ score: [mean ± SD] 45.3 ± 13.4) (Berthier, 2005) and because they had relatively homogeneous lesion locations on MRI scans.

CASE DESCRIPTIONS

Patient RRM. This patient was a 51-year-old right-handed male, who left school at 15 and had previously been a newspaper worker. He suffered a large left fronto- temporo-parietal infarction 17 months before trial enrolment. In the acute post- stroke period, he had a right hemiparesis and global aphasia which gradually evolved to a severe CA with mild apraxia of speech. Aphasia therapy during one year (two sessions a week) partially improved auditory comprehension and non-fluent speech production. On baseline evaluation with the Western Aphasia Battery (WAB) (Kertesz, 1982), his language deficits were consistent with CA. RRM's speech was dysfluent and contaminated by word retrieval problems, neologisms, phonological and formal errors (Table 1). Further testing with selected subtests of the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA) (Kay et al., 1995) disclosed a relative preservation of auditory comprehension (words, lexical decisions and sentences) but input phonology (auditory minimal word and non-word pairs) was abnormal. Picture naming was moderately impaired. Word repetition, though impaired, was less affected than non-word and digit repetition. Sentence repetition was moderately impaired.

Patient VRG. This patient was a 52-year-old right-handed male, who left school at 16 and had previously worked as an administrative. He suffered a large left fronto-temporo-parietal infarction 22 months before referral for the present trial. In the acute period, he had a right hemiparesis and global aphasia. He gradually recovered with speech-language therapy and physiotherapy, but on referral to our unit, he had a dystonic right hand and foot posture and a moderate CA (Table 1). On the WAB, his speech was fluent and free of phonological paraphasias but showed word retrieval problems and occasional formal errors. Further testing with PALPA subtests disclosed a relative preservation of auditory comprehension (lexical decisions and words) except for discriminating minimal word and non-word pairs and sentence comprehension. Picture naming was preserved. Word repetition was mildly impaired but much better than non-word and digit repetition. Sentence repetition was moderately impaired.

Patient JTO. This patient was a 72-year-old right-handed male who suffered a left fronto-temporo-parietal infarction 13 months before referral for participating in this drug trial. He had worked as an attorney until his retirement at age 65. In the acute post-stroke phase, he showed a rapidly resolving right hemiparesis and a global aphasia. Aphasia therapy (two sessions a week) was beneficial but gains reached a plateau after 6 months of treatment. On baseline evaluation, he had a moderate CA (see Table 1). On picture description from the WAB, his speech was fluent and free of phonological paraphasias. However, his utterances were punctuated by word retrieval problems, formal, perseverative and semantic errors. On PALPA subtests, he had a relative preservation of auditory comprehension (lexical decisions and words), except for discriminating minimal word and non-word pairs and sentence comprehension. Picture naming was moderately impaired. Word repetition was mildly impaired but much better than non-word and digit repetition. Sentence repetition was impaired.

Table 1| Background language testing.

Test	RRM	VRG	JTO
Western Aphasia Battery			
Aphasia Quotient (range: 0 - 100)	61.6	76	79.8
Information content (max: 10)	7	8	9
Fluency (max: 10)	$5^{\S}$	6	8
Comprehension (max: 10)	9.7	9.3	9.1
Repetition (max: 10)	4.6	4.2	6
Naming (max: 10)	4.5	8.5	7.8
PALPA			
Nonword Minimal Pairs (n = 56)	46 (.82)	47 (.84)	41 (.73)
Word Minimal Pairs (n = 56)	48 (.86)	48 (.86)	46 (.82)
Auditory Lexical Decision (n = 160)	154 (.96)	150 (.94)	148 (.92)
Repetition, Syllable Length (n = 24)	17*	21**	20***
Repetition: Nonwords (n = 24)	7	9	10
Spoken Word - Picture Matching (n = 40)	40 (1.0)	40 (1.0)	38 (.95)
Spoken Sentence - Picture Matching (n = 60)	55 (.92)	49 (.87)	48 (.80)
Naming by Frequency (n = 60)	30 (.50)	54 (.90)	45 (.75)
Digit Production	2	3	2

Patients are arranged in order of Aphasia Quotient scores derived from four subtests (spontaneous speech, comprehension, repetition, and naming). The combination of fluent speech production (WAB fluency score ≥ 5), relatively preserved comprehension (WAB comprehension score > 7) and impaired repetition (WAB repetition score < 6.9) indicates conduction aphasia.

§ This patient additionally had mild apraxia of speech (Ardila & Roselli, 1990). His verbal production was less fluent than usually reported (Broca-like CA) (Song, Dornbos, Lai, Zhang, Li, Chen, & Yang, 2011). Word repetition versus non-word repetition: * $p = 0.01$; ** $p = 0.001$; ***$p = 0.008$ (Fisher Exact Test, two-tailed).

Neuroimaging. MRIs at the chronic stage were performed in all three patients on different 1.5-T scanners. Areas of infarctions were manually drawn on representative axial slices (templates 3, 12, 18, 26) from the MRIcron software (www.mccausland-center.sc.edu/mricro/mricron) (Rorden, 2005). Lesion mapping was done by a radiologist (RR-C) who was blind to patients' demographic and clinical information using a modification of the methodology described by Gardner et al. (Gardner et al., 2012). Lesion size was estimated by overlying a standardised grid of squares (square area .1225 cm) onto each patient's template of the left hemisphere (grid area: 10.29 cm) and working out the percentage of squares damaged relative to undamaged parts of the left hemisphere (Gardner et al., 2012). Total or partial involvement of cortical and subcortical regions was registered (Table 2), and Brodmann's areas involved by the lesions were identified in every patient with the aid of the Brain Voyager Brain Tutor (www.brainvoyager.com/BrainTutor.html). Regions of ischaemic gliosis surrounding the infarctions were also drawn on the basis of increased signal in T2- weighted images. The relative involvement of perisylvian white matter tracts (AF and IFOF) was estimated using an atlas of human brain connections (Catani & Thiebaut de Schotten, 2012).

Large parts of the left middle and superior temporal gyri, supramarginal gyrus, dorsal insula and white matter corresponding to the dorsal stream (AF) were severely damaged in all patients. The ventral insula (posterior and middle parts) through which the ventral stream (IFOF) runs was severely damaged in two patients (RRM and JTO) and mildly affected in the remaining patient. Patient RRM had the more severe aphasia and the largest area of damage due to a frontal extension of the infarct, whereas less severe aphasia and relatively smaller lesions were documented in patients VRG and JTO. Further details of the patients' lesions are shown in Table 2 and Figure 1.

Table 2 | Lesion analysis

Patient	% of damage[a]	STG *BA 22*	*41*	*42*	MTG *BA 21*	ITG *BA 20*	AG *BA 39*	SMG *BA 40*	POT *BA 37*	DLPFC *BA 9/46*	orbIFG *BA 47*	trIFG *BA 45*	opIFG *BA 44*	Ventral insula	Dorsal insula	Dorsal stream	Ventral stream	Basal ganglia
RRM	27	2	2	2	2	-	1	2	-	- -	-	1	1	1	2	2	2	1
VRG	14.3	2	2	2	2	-	-	2	-	- -	-	1	1	-	2	2	1	1
JTO	14.1	2	2	2	2	-	-	2	-	- -	-	-	-	2	2	2	2	1

Quantification of lesion location: 2 = complete involvement/serious damage to cortical/subcortical region; 1 = partial involvement/mild damage to cortical/subcortical region. Abbreviations of cortical regions: STG = superior temporal gyrus; ITG = inferior temporal gyrus; AG = angular gyrus; SMG = supramarginal gyrus; POT = posterior occipito-temporal area; DLPFC = dorsolateral prefrontal cortex; orbIFG = pars orbitalis of the inferior frontal gyrus; trIFG = pars triangularis of the inferior frontal gyrus; opIFG = pars opercularis of the inferior frontal gyrus. [a]Lesion size was estimated by overlying a standardized grid of squares onto each patient's template and working out the percentage of squares damaged relative to undamaged parts of the left hemisphere (Gardner et al.,2012).

STUDY DESIGN

As already stated, language data from these three patients were initially included in a group analysis together with data from the other eight patients (total sample = 11) (Berthier et al., 2003). For the present case-series study, data from the initial phase (weeks 0 to 16), washout (weeks 16 to 20) and extension phase (weeks 20 to 28) were analysed in an individual basis, except for treatment effects which were analysed as a group using Cohen’s d statistics (Cohen, 1988). Therefore, a within-patient design, with baselines across behaviours and a washout period was adopted (Gast & Ledford, 2009). An A1-BC-A2-BD was used wherein A1 represented the initial base-line testing, BC was the combination of DP with DSLT, A2 was a new baseline after the washout period and BD was the combination of DP with MSRT. Multiple baseline evaluations before initiating the trial were not performed because language deficits in all patients were considered stable by virtue of their long aphasia duration (>1 year) and because they had reached a plateau with previous interventions which motivated referral for participation in the trial. The analysis of an A1-BC-A2-BD design led to three treatment comparisons, and three effect sizes were computed to represent the three demonstrations of experimental effect. These effect sizes relate to the phase comparisons of A1-BC (baseline to the first intervention phase—week 0 vs. week 16), BC-A2 (the first treatment phase to the washout, second baseline—week 16 vs. week 20), and A2-BD (the second baseline to the second intervention phase— week 20 vs. week 28). Further comparisons between A1 and BD and BC and BD were performed. Language evaluations were performed at baselines A1 (week 0) and A2 (week 20) and at end points BC (week 16) and BD (week 28). The study was performed according to the Declaration of Helsinki and the protocol was approved by the Local Community Ethics Committee for Clinical Trials. This study was conducted as an independent research project funded by Pfizer/Eisai, Spain, and it was designed, conducted and controlled by the principal investigator (MLB).

DRUG TREATMENT

In both drug phases of the study, all patients received DP (5 mg once a day) during a four-week titration phase followed by a 12-week maintenance phase (week 4 to week 16) (BC) and by a four-week maintenance phase (week 24 to week 28) (BD). Drug treatment and aphasia therapy were interrupted during the washout period (week 20 to week 24). Compliance was determined at every visit by tablet counts. DP tablets were provided by Pfizer/Eisai, Spain. The detection of potential adverse events was monitored during the trial.

APHASIA THERAPIES

Distributed speech-language therapy (DSLT). All three patients received DSLT at the same rehabilitation centre and were treated by the same speech therapist. DSLT followed a syndrome-specific standard approach and the therapeutic repertoire ranged from exercises involving naming, repetition, sentence completion, following commands, spoken object-picture matching and conversations on topics of the patients' own choice (Basso, 2003; Basso, Forbes, & Boller, 2013; Pulvermüller et al., 2001). In this trial phase, patients received DP-DSLT during 16 weeks and the total hours of therapy was 40 (~2.30 h/wk).

Massed sentence repetition therapy (MSRT). MSRT consisted of sentence repetition exercises and these were practiced at home where the patients were required to repeat audio-taped sentences. Patients received explanations on how to perform MSRT and one training practice session by a speech therapist. There were two sets of 20 sentences similar to the ones used by Kohn et al. (1990). One set was composed of sentences rich in semantic content (substantives, verbs) (e.g., “The boy runs”), whereas the other set included sentences mainly composed of pronouns, verbs and functor verbs (e.g., “She thinks about everything”). Sentence length in both sets ranged from 2 to 7 words. In this phase, patients received DP-MSRT during 8 weeks and the total number hours of therapy was 40 (~ 1 h/day, 5 days a week).

Control sentences. To evaluate possible generalisation of gains provided by MSRT, patients were asked to repeat a control list of 60 sentences which were not included in the therapy sets. Sentences length also ranged from 2 to 7 words (e.g., “give me bread”; “the girl sleeps in the sofa”). Testing was conducted only at baseline A2 (week 20) and end point BD (week 28).

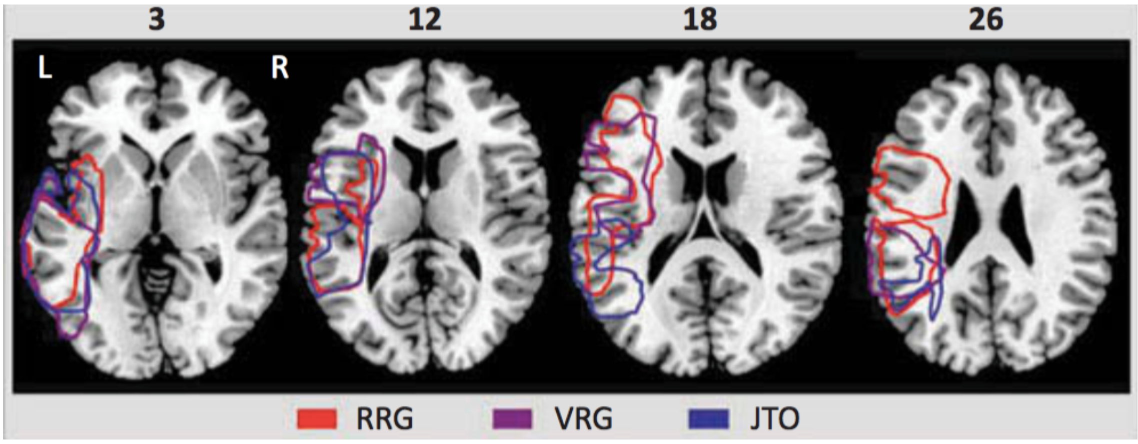

Figure 1. Representative axial slices (3, 12, 18, 26) from the MRIcron software (www.mccauslandcenter.sc. edu/mricro/mricron) (Rorden, 2005) depicting the full extension of lesions in each patient. See further details in text and lesion topography in Table 2.

OUTCOME MEASURES

Aphasia severity: WAB-aphasia quotient. To rate changes in the severity of aphasia the WAB-AQ was used. The WAB-AQ is a measure of aphasia severity which has been shown sensible enough to detect longitudinal changes in previous drug trials with different cholinesterase inhibitors (Berthier et al., 2003, 2006; Chen et al., 2010; Hong et al., 2012). Reductions in the WAB-AQ scores ≥ 5 at end points (BC and BD) in comparison to baselines (A1 and A2) were considered a positive response to the intervention (Berthier et al., 2011; Cherney et al., 2010).

Connected speech production. To examine connected speech production, speech samples in baselines and post-treatment phases were obtained from the picture description (picnic scene) of the WAB during a time limit of 5 minutes. All descriptions were audio-taped and transcribed. Since measures to rating spontaneous speech (fluency and information content) of the WAB are to a certain extent unreliable, speech samples were analysed for percentage of correct information units (%CIU) defined as non-redundant content words that convey correct information about the stimulus (Marchina et al., 2011; Nicholas & Brookshire, 1993; Zipse et al., 2012) using the following formula: number of CIUs/number of words × 100. According to Nicholas and Brookshire (1993) to be classified as CIUs, words should not only be intelligible in context, but also be accurate, relevant and informative with respect to the stimulus. Meaningless utterances, perseverations, paraphasias and other inappropriate information (exclamations) were counted as words, but not classified as CIUs.

REPETITION TASKS

Word and non-word repetition. Two subtests of PALPA were used. Repetition of words was assessed with the Repetition: Syllable Length (test 7), and non-words with the Repetition: Non-words (test 8).

Word pair repetition. To assess the effect on performance during word repetition when the memory load is increased, patients were required to repeat word pairs in three different conditions: (1) no delay direct (e.g., “house-flower”) (n = 55), (2) no delay inverted (e.g., “flower-house”) (n = 55), and (3) unfilled delay (after a delay of 5 seconds unfilled by the neither the patient or researcher) (n = 55) (Gold & Kertesz, 2001; Martin et al., 1996).

Word triplet repetition. To assess the influence of interventions on lexical-semantic information when the demand of the AVSTM is increased, all patients were asked to repeat word triplets. This task is a modification of the one used by McCarthy and Warrington (1987) in patients with CA. The present repetition battery included three lists of high-frequency words and three lists of low-frequency words (Berthier, 2001). Two sets of 60 three-word lists (verb-adjective-noun) were constructed. These were composed of word strings of increasing semantic richness that is from non-organised to organised semantic information. Two 20 three-word lists (List 1: 60 high-frequency words; List 4: 60 low-frequency words) consisted of random word combinations (e.g., “walk-shiny-pools”). Two other 20 three-words lists (List 2: 60 high-frequency words; List 5: 60 low-frequency words) conveyed loosely constrained meaningful informa- tion (e.g., “crawl-slow-baby”), and two other 20 three-word lists (List 3: 60 high- frequency words; List 6: 60 low-frequency words) conveyed closely constrained meaningful information (e.g., “eat-green-apple”). Words were read at a rate of one per second, and patients were required to repeat the words in the order given by the examiner. Responses were scored for the number of lists repeated verbatim in each condition and for the number of words repeated accurately as a function of serial position (initial, medial and final) in the list, irrespective of whether the list was repeated accurately or not.

Repetition of clichés and novel sentences. Patients with CA tend to show better performance on repeating novel sentences than idiomatic clichés, because they can access meaning during repetition of the former type of sentences (McCarthy & Warrington, 1984). To explore this dissociation, all three patients were asked to repeat familiar idiomatic phrases of Spanish (n = 40) taken from the 150 Famous Clichés of Spanish Language (Junceda, 1981) and a set of novel, control phrases (n = 40) that were constructed following the methodology described by Cum and Ellis (1999). Novel phrases were derived from the idiomatic phrases by replacing one to three content words in each phrase by other words matched in length of words and word frequency. Both sets of phrases (clichés and novel) were randomised and read aloud to patients one at a time.

Results- Study 1

APHASIA SEVERITY: WESTERN APHASIA BATTERY-APHASIA QUOTIENT

Individual analyses showed that the aphasia severity measured with the WAB-AQ improved significantly in comparison with baseline assessment (A1) with both interventions in all patients (DP-DSLT: RRM and VRG, $p < .001$; JTO, $p = .016$; DP-MSRT: RRM and VRG, $p <.001$, JTO, $p = .01$).3 Comparison of washout-baseline assessment (A2) with DP-MSRT (BD) showed significant gains in JTO ($p < .001$) and a strong trend for significance in both RRM and VRG ($p = .063$). Intervention with DP-MSRT (BD) was associated with better outcomes than DP-DSLT (BC) (mean increases on the WAB-AQ = 3.2), but differences did not reach statistical significance (Table 3).

CONNECTED SPEECH PRODUCTION

Post-interventions changes in percentage of CIUs relative to baseline (A1) were variable across patients. Patient RRM improved 14% with DP-DSLT and 70% with DP-MSRT; patient VRG improved 3% with DP-DSLT and 10% with DP-MSRT; and patient JTO decreased 8% with DP-DSLT and improved 13% with DP- MSRT. In patient RRM, who obtained the lower scores in speech production (WAB fluency: 5/10; WAB information content: 7/10) at baseline, remarkable improvements occurred after both interventions, but mostly with DP-MSRT. These improvements were less evident in VRG and JTO who had more fluent and informative verbal productions at baseline (see Tables 1 and 3).

WORD AND NON-WORD REPETITION

Baseline scores (A1) in Word Repetition, Syllable Length from PALPA (test 7) were mildly impaired in two patients (VRG, .88; JTO, .83) and moderately impaired in the other patient (RRM,.71). Word repetition was significantly better than non-word repetition in all three patients at baseline (A1) (Table 2). As expected, there were no significant changes in single word repetition after both interventions in both patients with mildly impaired performance at baseline (VRG and JTO, p ≥ .25) most likely due to ceiling effect, whereas a trend for improvement was seen after both interventions in the patient (RRG) with moderately impaired performance (both treatments, p = .063). All patients showed moderately impaired ability to repeat items of the Repetition: Non-words PALPA subtest (test 8) at baseline (A1). Numerically, all patients improved test performance with both interventions. A trend for significant improvement was only observed in JTO after both interventions (p = .063), whereas no changes were found in the remaining two patients.

DIGIT SPAN

No changes were seen with either therapy in all three patients (p = .1) (Table 2).

Table 3 | Results of language testing at baseline, endpoints and washout.

Measure	RRM				VRG				JTO			
	Baseline - (Wk 0)	DP/CSLT - (Wk 16)	Washout - (Wk 20)	DP/MSRT (Wk 28)	Baseline - (Wk 0)	DP/CSLT - (Wk 16)	Washout - (Wk 20)	DP/MSRT (Wk 28)	Baseline - (Wk 0)	DP/CSLT - (Wk 16)	Washout - (Wk 20)	DP/MSRT (Wk 28)
Western Aphasia Battery (WAB)												
Picture description												
% Correct information units [b]	13	29	25	83	80	87	77	90	78	70	87	91
Aphasia Quotient (max = 100) [a]	61.6	78.6	77.2	81.6	76	88.4	85	90	79.8	87	76.8	91.1
Repetition (max = 100) (WAB)	46	70	62	88	42	82	74	76	60	64	64	76
Word repetition (n = 24) (PALPA 7)	17	18	17	22	21	23	23	23	20	22	23	23
Nonword repetition (n = 24) (PALPA 8)	8	12	9	12	9	11	8	10	10	14	17	15
Digit production	2	3	3	3	3	3	2	3	2	2	3	3
Word list repetition												
Word pairs												
no delay direct (n = 55)	49	46	46	48	32	52	46	48	30	32	35	38
no delay inverted (n = 55)	45	49	48	48	38	48	45	51	34	38	35	40
unfilled 5 sec. delay (n = 55)	49	49	48	50	42	50	48	50	25	33	41	43
Triplets (high-frequency) (n = 60)												
Random word combination	0	6	7	12	5	6	6	10	2	4	5	7
Loosely constrained information	2	5	10	12	3	8	8	13	3	7	10	12
Constrained information	5	11	11	17	4	6	10	15	9	15	14	16
Triplets (low-frequency) (n = 60)												
Random word combination	1	8	6	10	0	0	0	9	1	2	4	4
Loosely constrained information	1	8	11	13	0	2	2	10	4	1	5	8
Constrained information	7	8	9	14	1	6	4	10	6	12	6	9
Sentence repetition												
Idiomatic clichès (max = 40)	4	8	6	9	12	15	16	17	17	25	23	24
Novel sentences (max = 40)	11	18	19	23	14	18	15	20	19	27	29	32
Therapy sentences (max 40)	NT	NT	20	39	NT	NT	21	37	NT	NT	22	38
Control sentences (max = 60)	NT	NT	30	44	NT	NT	34	47	NT	NT	35	47

Data from these patients were grouped and treatment effects were analysed using Cohen's d statistic (Cohen, 1988). [a]A_1 (baseline) versus BC (DP-DSLT): Cohen's d = 1.0 and A_2 (washout-baseline) versus BD (DP-MSRT): Cohen's d = 1.2. WAB-AQ: BC (DP-MSLT) versus BD (DP-MSRT), Cohen's d = 1.3. [b]A_1 (baseline) versus BD (DP-MSRT): Cohen's d = 1.14, A2 (washout-baseline) versus BD (DP-MSRT): Cohen's d = 1.05, BC (DP-CSLT) versus BD (DP-MSRT): Cohen's d = 1.22. A Cohen's d effect size of .2 to .3 might be a "small" effect, around .5 a "medium" effect and .8 to infinity, a "large" effect (Cohen, 1988).

WORD PAIR REPETITION

No delay direct. At baseline evaluation, one patient had mildly impaired performance (RRM, .89), whereas the other two patients had moderately impaired performance (VRG, .58; JTO, .54). Patient VRG significantly improved with both DP- DSLT (BC) and DP-MSRT (BD) relative to baseline evaluation (A1) (p = .001), but there were no differences between therapies. His scores in post-washout evaluation (baseline A2) were significantly better than in baseline evaluation (A1), and performance after DP-MSRT (BD) were also significantly better than post-washout evaluation (A2) (p = .031). In patient JTO, DP-DSLT (BC) showed a trend for improvement in comparison with baseline (A1), and a significant improvement with DP-MSRT (BD) was found in comparison with both baseline (A1) (p = .008) and washout-baseline (A2) evaluations (p = .031). No changes were found in patient RRM most likely due to ceiling effect.

No delay inverted. Baseline evaluation revealed that one patient had mildly impaired performance (RRM, .81), whereas the other two patients had moderately impaired performance (VRG, .69; JTO, .61). Patient VRG improved with both DP- DSLT (BC) (p = .002) and DP-MSRT (BD) (p = .001), but there were no differences between interventions. His scores in washout evaluation (A2) were significantly better than that in baseline evaluation (A1) (p = .016), and scores after DP-MSRT (BD) were better than those obtained in washout-baseline (A2) evaluation (p = .031). Patient JTO only improved with DP-MSRT (CD) relative to baseline evaluation (A1) (p = .008), and gains with this intervention were significantly better than those obtained with DP-DSLT (BC) (p = .031). Scores in this patient also showed a trend for improvement after DP-DSLT (BC) in comparison with baseline evaluation (A1) (p = .063). Patient RRM did not show improvements with either therapy most likely due to ceiling effect.

Unfilled 5-second delay. At baseline evaluation, two patients had mild to moderate impaired performance (RRM, .89; VRG, .76), whereas the other patient had severely impaired performance (JTO, .45). Patient VRG showed significant improvements with both therapies relative to baseline evaluation (A1), with better scores after DP- MSRT (BD) (p = .004) than after DP-DSLT (BC) (p = .008). However, there were no differences between these two interventions. In this patient, scores after washout (A2) were significantly better than those obtained in baseline evaluation (A1) (p = .031). Scores in patient JTO significantly improved with both DP-DSLT (BC) (p = .008) and DP-MSRT (BD) (p = .001) relative to baseline evaluation (A1), but gains were significantly better with DP-MSRT (BD) than with DP-DSLT (BC) (p = .002). Scores after washout (baseline A2) were significantly better than those obtained at baseline (A1) (p = .001) and after DP-DSLT (BC) (p = .008). No changes were found in patient RRM with either therapy possibly due to ceiling effect.

WORD TRIPLET REPETITION

The number of word triplets repeated accurately by these three patients in each condition is shown in Table 3 and according to serial position in Figure 2. Treatment with DP-DSLT (BC) significantly improved all high-frequency word triplets (Lists 1–3) in comparison with baseline (A1) in two patients (RRM, p < .001; VRG, p = .008) but not in the other patient (JTO, p = .125). As expected, analyses of all low-frequency word triplets (Lists 4–6) revealed less robust gains than in repetition of high-frequency word strings, but again there were significant improvements with DP-DSLT (BC) relative to baseline (A1) in two patients (RRM, p = .031; VRG, p = .016) and no changes in the other patient (JTO, p = .125). Comparisons of all high-frequency word triplets (Lists 1–3) between baseline (A1) and washout (baseline A2) revealed significantly better performance in post-washout evaluation (A2) in two patients (RRM, p <.001; VRG, p = .031). No changes were found in the remaining patient (JTO, p = .125). Differences in repetition of all low- frequency word triplets (Lists 4–6) between baseline (A1) and washout (A2) revealed significantly better performance in post-washout evaluation (A2) in one patient (RRM, p < .001), a trend for improvement in another (VRG, p = .063) and no changes in the remaining patient (JTO, p = .125).

After treatment with DP-MSRT (BD) word triplet repetition was significantly better than scores at baseline evaluation (A1) in all patients in the repetition of both high-frequency strings (Lists 1–3) and low-frequency strings (Lists 4–6) (all patients, p <.005). Similar results were found when repetition of high-frequency and low- frequency triplets after treatment with DP-MSRT (BD) was compared with scores at post-washout testing (A2) in all patients (RRM and VRG, in both measures p ≤ .001; JTO, in both measures p = .031). Importantly, combined intervention with DP-MSRT (BD) significantly improved performance in repetition of high- frequency word triplets in comparison with scores after DP-DSLT (BC) in all patients (both RRM and VRG, p < .001; JTO p = .031) and in repetition of low-frequency word triplets in two patients (VRG, p <.001; JTO p = .031). There was a trend for improvement in the remaining patient (RRM, p = .063). Finally, results were even more robust when all lists (1–6) were analysed together. Patients' performance with DP-DSLT were significantly better than the ones obtained at baseline (A1) (all patients, p < .001) and scores after DP-MSRT were significantly better than those obtained at baseline (A1) and post-washout (A2) testing (all patients in both evaluations, p <.001). Scores after DP-MSRT (BD) were better than those obtained with DP-DSLT (BC) (all patients, p < .001).

Changes induced by both interventions in the repetition of word triplets were also analysed taking into consideration the semantic relatedness of word strings, so that the following triplets were analysed: random word combination (Lists 1 and 4), loosely constrained information (Lists 2 and 5) and constrained information (Lists 3 and 6). For the sake of simplicity, high-frequency and low-frequency triplets were analysed together. Repetition of word triplets containing random word combination (Lists 1 and 4) improved with DP-DCSL relative to baseline (A1) only in one patient (RRM, p <.001). Treatment with DP-MSRT (BD) provided greater improvement than DP-DSLT in two patients (RRM, p = .008; VRG, p < .001), and a trend for improvement was seen in the remaining patient (JTO, p = .063). Scores after DP- MSRT (BD) were significantly better than the ones in washout testing (A2) in two patients (RRM, p = .004; VRG, p <.001) and better than baseline (A1) in all three patients (RRM and VRG, both p = .004; JTO, p < .008). Repetition of word triplets containing loosely constrained semantic information (Lists 2 and 5) improved with DP-DCSL relative to baseline in two patients (RRM, p = .002; VRG, p <.016). Treatment with DP-MSRT (BD) provided greater improvement than DP-DSLT in all patients (p = .001). Scores after DP-MSRT (BD) were significantly better than the ones in washout testing (A2) in one patient (VRG, p < .001) and also better than baseline (A1) in all patients (p <.001). Finally, repetition of word triplets containing constrained semantic information (Lists 3 and 6) improved with DP-DCSL relative to baseline in all patients (RRM and VRG, p < .016; JTO, p <.001). Treatment with DP-MSRT (BD) provided greater improvement than DP-DSLT two patients (RRM and VRG, p = .001). Scores after DP-MSRT (BD) were significantly better than the ones in washout testing (A2) in two patients (RRM and VRG, p < .001) and also better than baseline (A1) in all patients (p <.001). Changes in serial position were noted (Figure 2). At baseline, all patients showed primacy and recency effects; items occurring in the initial and final position were repeated better than items in medial positions. After DP-DSLT, one patient RRM significantly improved performance in positions 2 and 3 in high-frequency words and all positions in low-frequency words (all, p < .005), whereas another patient (VRG) improved positions 1 and 2 with this therapy and position 1 with DP-MSRT (all p = .0001).

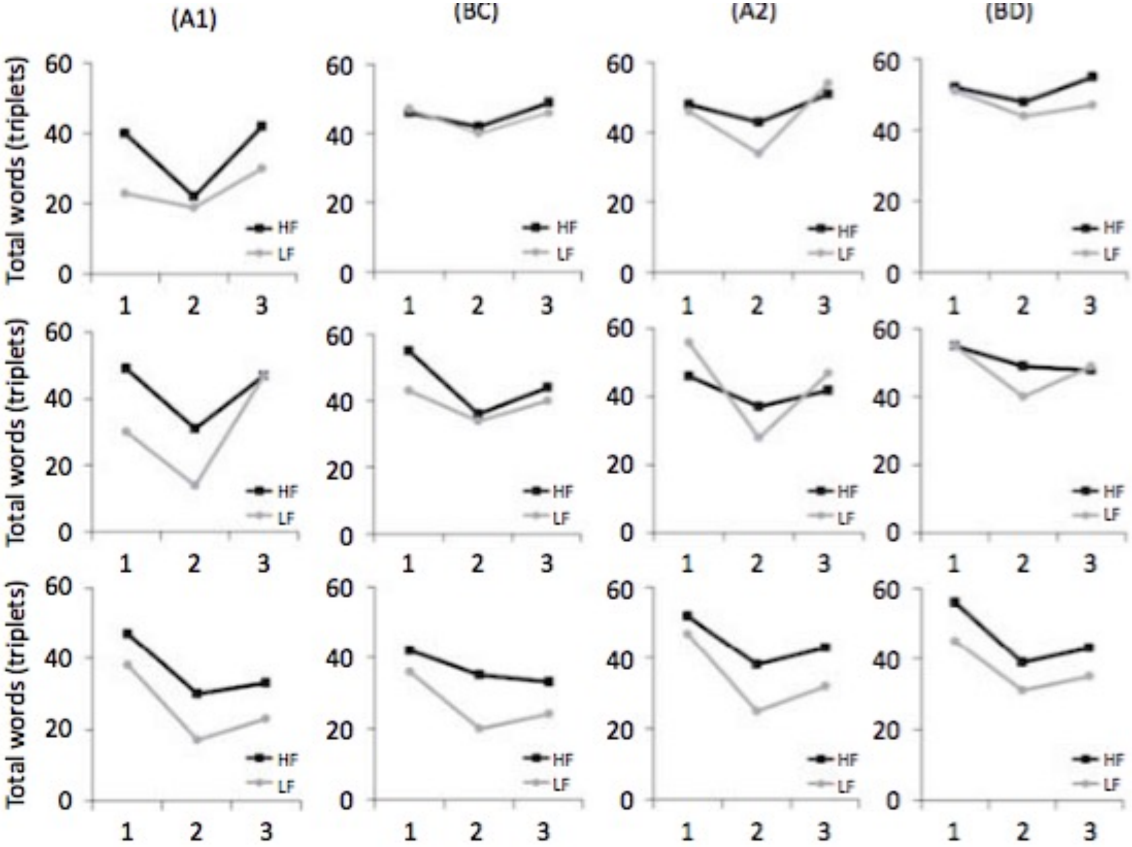

Figure 2. Number of words correctly repeated as function of frequency and serial position in triplets. Graphs depict performance of individual patients (top panel: RRG; medial panel: VRG; and bottom panel: JTO) during repetition of high-frequency (HF) and low-frequency (LF) triplets at baselines (A_1 and A_2) and end points (BC and BD) evaluations. HF triplets included three lists (1, 2 and 3), whereas the remaining three lists (4, 5 and 6) were included in LF triplets. Therefore, the total number of words in each position was 60. See further details in text.

CLICHÉS AND NOVEL SENTENCES

Numerically, all patients showed better baseline performance on repeating novel sentences than clichés although differences did not reach significance. After interventions RRM and VRG did not show improvement in cliché repetition with either intervention, whereas JTO improved his performance in this task with both DP-DSLT (p = .008) and DP-MSRT (p = .016). However, there were no changes when DP-MSRT was compared with washout testing (A2). As expected, better out- comes were found in repetition of novel sentences in two patients with DP-DSLT compared with baseline (A1) (RRM, p = .016; JTO, p = .008), and even more robust benefits were found in all three patients when DP-MSRT was compared with baseline (A1) (RRM and JTO, p <.001; VRG, p = .031). No changes were found, however, when intervention with DP-MSRT was compared with washout testing (A2).

THERAPY AND CONTROL SENTENCES

Table 3 shows patients' performance on repetition of therapy and control sentences. Scores after DP-MSRT (BD) were significantly better than those obtained at wash- out (A2) in all three patients in both therapy sentences (all, p < .005, Fisher Exact Test, two-tailed) and control sentences (all, p <.05, Fisher Exact Test, two-tailed).

Discussion- Study 1

In this case-series study, we did find that both treatments (DP-DSLT and DP-MSRT) improved repetition of word lists and therapy and control sentences with generalisation of gains to aphasia severity and connected speech during picture description. The combination of DP with MSLT provided better results in connected speech during picture description and word list repetition than DP combined with a less-intensive therapy administered during a longer period (DSLT). Importantly, our patients received the same number of hours (40 hours) of aphasia therapy administered with different timetables (16 weeks of DSLT and 8 weeks of MSRT) and separated between them by a washout period (4 weeks). Furthermore, DSLT trained different language domains (naming, repetition, sentence completion, following commands, spoken object-picture matching and conversations), whereas MSRT trained only a single language domain (sentence repetition). Treatment with DP was safe and well tolerated at usual doses. Only one patient (RRM) developed mild irritability and right leg muscle cramps that not required drug discontinuation. Before advancing further in the discussion, let us examine the theoretical and clinical justification that encouraged us to use MSRT in this case-series study.

DONEPEZIL AND MASSED SENTENCE REPETITION THERAPY

The treatment with MSRT was selected on the basis of previous studies (see Introduction) and clinico-anatomical relationships documented in our patients. In the acute stroke period, our three patients had global aphasia secondary to large left perisylvian infarctions. Aphasia severity gradually improved, and when participants were formally evaluated for inclusion in the present trial (mean aphasia duration: 17.3 months), the pattern of language deficits was consistent with the diagnosis of CA (Berthier et al., 2014; Kertesz, 1982; Kohn, 1992). Further baseline cognitive testing of language in these patients revealed impaired/preserved language functions and a pattern of errors (e.g., phonological paraphasias in single word repetition and formal and semantic paraphasias in word list repetition) that placed their syndromes in the phonological-deep dysphasia continuum (Jefferies et al., 2007; Martin, 1996; Wilshire & Fisher, 2004). The occurrence of these deficits affecting the storage capacity of phonological and lexical-semantic processes in conjunction with extensive damage involving the left dorsal and ventral auditory streams concurs with the hypothesis suggesting that residual repetition in these disorders reflects partial reliance on right hemisphere activity (Berthier et al., 2012; Demeurisse & Capon, 1991).

Recent studies in Wernicke’s aphasics reveal dual acoustic-phonological and semantic breakdowns correlating with left temporo-parietal involvement (Robson et al., 2012; Robson et al., 2012). Our patients also had lesions involving these posterior cortical sites, yet their baseline performance in certain phonological and lexical-semantic processing tasks ranged from mildly impaired to normal. The mildness of these receptive deficits most likely reflects the consecutive beneficial effect of both spontaneous improvement and aphasia therapy prior to trial inclusion via restitutive integration of non-damaged areas of the left hemisphere, the right hemisphere or both (Fernandez et al., 2004; Harnish et al., 2008; Weiller et al., 1995). Potential candidate regions in the left hemisphere for mediating recovery are the prefrontal-parietal (angular gyrus) cortices (Meltzer et al., 2013; Sharp et al., 2010) and basal ganglia (Harnish et al., 2008). Nevertheless, the role of these areas in recovery cannot be accepted in a straightforward way because patient RRM had partial damage to the prefrontal and angular cortices and all patients had severe damage to areas encompassing the superior longitudinal fasciculus linking these distant cortical sites. The role of left basal ganglia could not be discarded, however, as all patients had only mild involvement of the left putamen and functional neuroi- maging in the female CA patient reported by Harnish et al. (2008) with a larger involvement of left basal ganglia, which revealed that she was capable of activating some spared parts of the striatum after massed aphasia therapy. Brain activation after distributed therapy was less noticeable (Harnish et al., 2008). Although functional neuroimaging could not be performed in our patients to examine the spontaneous and treatment-induced compensatory reorganisation of these functions, our findings in anatomical MRI suggest a prominent role of the right hemisphere reorganisation after distributed and massed therapies combined with DP.

We did find that DP-MSRT provided significantly better outcomes than DP- DSLT in most repetition subtests (word pairs, word triplets and novel sentences). Sentences practiced during DP-MSRT also improved, and there was a generalisation of gains to untreated control sentences. We also did find medium to large treatment effects for DP-MSRT in comparison with baselines (A1, A2), and DP-CSLT (BC) in aphasia severity (WAB-AQ), and connected speech (%CIUs) with DP-MSRT. Improvement in some of these tasks implies a generalisation of benefits triggered by DP-MSRT, which is in consonance with the results reported in previous intervention studies of CA exclusively treated with repetition training (Kalinyak-Fliszar et al., 2011; Koening-Bruhin & Studer-Eichenberger, 2007; Kohn et al., 1990; Majerus et al., 2005). Nevertheless, findings from the present trial are not fully comparable with previous studies because we augmented the benefits provided by MSRT with a drug. Our findings emphasise the usefulness of implementing neuroscientifically based therapies, like MSRT (and MIT), which are specifically intended to recruit the activity of normal brain structures (right AF) to compensate the function of their homologues in the damaged hemisphere (Schlaug et al., 2009; Zipse et al., 2012).

MECHANISMS UNDERPINNING RECOVERY WITH DONEPEZIL COMBINED WITH MASSED SENTENCE REPETITION THERAPY

Experimental studies in rodents indicate that acetylcholine promotes synaptic transmission, stimulate synaptic plasticity and coordinates the activity of groups of neurons in response to internal and external stimuli eventually enhancing perception, attention, learning and memory processes (Picciotto et al., 2012; Sarter et al., 2003, 2005). Cholinergic stimulation in experimental conditions facilitates neuroplasticity, and the resulting changes are more apparent when cholinergic modulation is paired with training (experience-dependent plasticity) (Kleim & Jones, 2008; Sarter et al., 2003, 2005). Human neuroimaging studies of the cholinergic systems substantiate and extend physiological accounts of cholinergic function reported in experimental animal studies (see Bentley et al., 2011).

Although we did not perform functional neuroimaging in these three patients, our results invite speculations on the role of DP-MSRT in modulating dysfunctional and underused networks. At baseline, impaired performance on word list and sentence repetition in our patients may be ascribed to synaptic depression in the left lateral cholinergic pathway (insula and fronto-parietal white matter)

(Buckingham & Buckingham, 2011; Gotts, et al., 2002; Gotts & Plaut, 2004; McNamara & Albert, 2004; Selden et al., 1998; Tanaka et al., 2006) with incomplete compensation of deficits by the right perisylvian white matter tracts. We suggest that cholinergic enhancement with DP boosted aphasia therapy effects not only by reverting synaptic depression in dysfunctional areas of the left hemisphere but, more importantly, by recruiting right perisylvian pathways. Recent intervention studies in chronic aphasia demonstrated that benefits in speech production with MIT (Schlaug et al., 2009; Zipse et al., 2012) and in repetition and naming with CIAT (Breier et al., 2011) were associated with functional and structural plasticity of the right AF. We suggest that MSRT (and to a lesser extent DSLT) in combination with DP might also recruit right hemisphere networks. After both treatments, our patients reacquired the ability to repeat with ease previously inaccessible target words in both lists and novel sentences. They also recovered the retention of word order as reflected by significant increment in the number of correct repetition of word triplets and sentences. This may have resulted from reversion of synaptic depression (Gotts & Plaut, 2002) and reduction of spreading activation of competitors (Foster et al., 2012) induced by DP. Also, it is tempting to argue that increased neural efficiency and better task performance promoted by cholinergic stimulation (Ricciardi, et al., 2013) were enhanced further with MSRT aimed to strengthen the activity of right hemisphere perisylvian white matter tracts (AF) previously underused in the service of speech repetition. Furthermore, cholinergic enhancement might also have modulated fronto-parietal regions implicated in executive-attentional processes (Demeter & Sarter, 2013) as well as attention and AVSTM through a dynamic interaction between right dorsal and ventral auditory streams (Majerus et al., 2012).

Recovery of production deficits in patients with fluent aphasia generally follows a fixed sequence (e.g., Kertesz, 1984; Kohn et al., 1996) evolving from initial production of target-related neologisms, phonological errors and omissions followed by better identifiable phonological and formal errors and eventually progressing to below-average or normal performance. Benefits provided by combined interventions in our three patients were at variance with the usual pattern of recovery from CA described in chronic cases because both interventions circumvented these seemingly obligate steps of recovery. Moreover, we found that DP-MSRT augmented and speeded up recovery in comparison with both DP-DCSLT.

LIMITATIONS

Our intervention trial has the shortcoming of using an open-label, within-subject design implementing two successive treatments. Indeed, one drawback of this design is the increased likelihood of residual beneficial effects of treatment with DP-DSLT on the outcome of DP-MSRT treatment (carryover effect) (Grady et al., 2001). Nonetheless, to minimise the impact of the carryover effect on the outcomes of DP-MSRT, we introduced a four-week washout period between both interventions. Despite the introduction of this non-intervention period, post-washout performance (A2, week 20) in all patients remained well above the scores obtained at baseline (A1, week 0). Several hypotheses have been advanced to account for this persistent improvement (Berthier et al., 2003, 2006; Code et al., 2010; FitzGerald et al., 2008; Hughes et al., 2000), and some of them are related to the use of DP. The first argument maintains that the persistence of gains in cognition after a washout period of 4 weeks may depend on the long plasma half-life of DP (~104 hours) (FitzGerald et al., 2008). Another hypothesis, more compelling than the previous one, suggests that DP promotes brain plasticity in language and short-term memory systems and that these neuroplastic changes persist after DP withdrawal (Berthier et al., 2003, 2006; FitzGerald et al., 2008; Hughes et al., 2000). A complimentary piece of information unrelated to DP treatment refers to the role of delayed beneficial effect of aphasia therapy after its interruption in chronic aphasic patients (Code et al., 2010). It is also worth emphasising in defence of the benefits provided by DP-MSRT that although our patients received the same number of hours of aphasia therapy (40 hours) administered with different timetables, the duration of the drug treatment during DSLT was actually the double (16 weeks) than the one received by patients during MSRT (8 weeks). This suggests that the addition of DP to MSRT increased and speeded up recovery in comparison with DP-DSLT. Finally, our participants' expectation and motivation generated by their participation in a trial with a new pharmacological treatment of aphasia may have played a role in improvement. Even though participants remained motivated throughout the whole trial, in our experience the great expectation for improving depends more on the initial response to pharmacological treatment than the addition of an alternative rehabilitation technique (e.g., MSRT) in the last phase of the trial. Therefore, if our belief is correct, one can expect a greater impact of motivation on outcomes in the initial (DP-DSLT) rather than in final phase (DP-MSRT) of the trial.

STUDY 2: A case of crossed conduction aphasia.

Reference: ***De-Torres, I.,*** *Dávila, G., Berthier, M.L., Walsh, S.F., Moreno-Torres, I., & Ruiz-Cruces, R. (2013). Repeating with the right hemisphere: reduced interactions between phonological and lexical-semantic systems in crossed aphasia? Frontiers in Human Neuroscience, Oct 18; 7: 675.*

Abstract - Study 2

Speech production and communication deficits were studied in a single-case male patient (JAM) with crossed aphasia (aphasia after right hemisphere) and the neural correlates of were also examined with neuroimaging. Repetition performance was widely assessed in a patient with crossed CA and a striatal/capsular vascular lesion encompassing the right AF and inferior frontal-occipital fasciculus (IFOF), the temporal stem and the white matter underneath the supramarginal gyrus. JAM showed lexicality effects repeating better words than non-words, but manipulation of other lexical-semantic variables exerted less influence on repetition performance. Imageability and frequency effects, production of meaning-based paraphrases during sentence repetition, or better performance on repeating novel sentences than overlearned clichés were hardly ever observed in this patient. DTI disclosed damage to the right long direct segment of the AF and IFOF with relative sparing of the anterior indirect and posterior segments of the AF, together with fully developed left perisylvian white matter pathways. Communication in activities of daily living (amount and quality) were reduced. Altogheter, these findings suggest (1) that striatal/capsular lesions extending into the right AF and IFOF in some individuals with right hemisphere language dominance are associated with atypical repetition patterns which might reflect reduced interactions between phonological and lexical-semantic

processes; and (2) that patients with crossed CA can also display reduced communication abilities in spite of having fluent spontaneous speech.

Introduction - Study 2

It is well-established that the majority (95%) of right-handeds have their left cerebral hemispheres dominant for language (Annett, 1998; Wada & Rasmussen, 2007). A minority (5%) of right-handeds have right hemispheric specialization for language (Loring et al., 1990; Annett, 1998; Pujol et al., 1999; Knecht et al., 2002) and mixed language dominance (language production and reception represented in different hemispheres) which can occur in both normal (Lidzba et al., 2011) and brain damaged right-handeds (Kurthen et al., 1992; Paparounas et al., 2002; Kamada et al., 2007; Lee et al., 2008) is even more infrequent. The rarity of complete or incomplete lateralization of language to the right hemisphere explains why only a minority of right-handed individuals develop language deficits after right hemisphere injury (crossed aphasia) (Bramwell, 1899; Alexander et al., 1989a; Mariën et al., 2001, 2004). Although crossed aphasia is rare, analysis of language functioning in these subjects represents an ideal opportunity to examine whether their language performance and neural architecture underpinning language functions in the right hemisphere are the same as those reported in subjects with left hemisphere language dominance (Catani et al., 2007; Turken & Dronkers, 2011; Catani & Thiebaut de Schotten, 2012). Here, we report the occurrence of fluent aphasia with severely abnormal repetition and deficits in sentence comprehension (CA) in a patient who suffered a large right subcortical stroke lesion. This clinical-anatomical correlation is uncommon, but its description can further illuminate the neural organization of propositional language in the right hemisphere. In an attempt to accomplish this, in the present study the localization of damage to white matter tracts underpinning language repetition was outlined in one patient with the aid of brain sections depicted in an atlas of human brain connections (Catani & Thiebaut de Schotten, 2012) and with DTI of bilateral white matter tracts.

Knowledge on the organization of propositional language in the right hemisphere comes from the analysis of aphasic patients with damage to the right hemisphere (see Alexander et al., 1989a; Mariën et al., 2004) and from a case series study of intraoperative cortical-subcortical stimulation (Vassal et al., 2010). Vassal and coworkers (2010) performed intraoperative cortical-subcortical electrical functional mapping in three right-handed adults who had right-sided low-grade gliomas. Right hemisphere language dominance was variously demonstrated by identification of language deficits during both partial epileptic seizures and preoperative formal testing, and activations in functional magnetic resonance imaging (fMRI) (one patient). During surgical interventions reproducible language disturbances were found by stimulating cortical sites in frontal and temporal cortices. Electrostimulation of the inferior fronto-occipital fasciculus (IFOF) elicited semantic paraphasias, whereas stimulation of the AF caused phonemic errors, thus supporting in these cases the hypothesis of a mirror organization of white matter tracts between right and left hemispheres (Vassal et al., 2010).

Studying patients with crossed aphasia, Alexander and colleagues, defined two clinical-radiological correlations which were named “mirror image” and “anomalous” (Alexander et al., 1989a; Alexander & Annett, 1996; Alexander, 1997; Mariën et al., 2004). The “mirror image” pattern assumes that the right language cortex has a similar structure and connections to the classical left language cortex, and therefore, similar language deficits to the ones observed after left hemisphere injury can be expected when the same injury occurs in homologous areas of the right hemisphere (Henderson, 1983; Bartha et al., 2004). This pattern occurs in as many as 60% patients and all clinical types of aphasia have been described (see Mariën et al., 2001, 2004). By contrast, the "anomalous" pattern considers that the structural arrangements and functional organization of the language cortex in the right hemisphere are different to the ones in the left language cortex, so that atypical language deficits can occur after right hemisphere injury (e.g., Wernicke's aphasia associated with frontal damage). The anomalous pattern has been described in approximately 40% of patients and it can be easily identified when patients present with relatively isolated phonological or lexical-semantic deficits associated with large lesions in the right perisylvian area (Alexander et al., 1989a; Mariën et al., 2001, 2004). Interestingly, the association of CA with an atypical location is more commonly encountered with right hemisphere lesions (35%) than after left hemisphere involvement (13%) (Basso et al., 1985; Alexander et al., 1989a; Dewarrat et al., 2009). Despite the relatively frequent occurrence of CA in cases of both "mirror image" (Henderson, 1983; Bartha et al., 2004) and "anomalous" crossed aphasia (Alexander et al., 1989a) comprehensive analyses of its main deficits (repetition, short-term memory, sentence comprehension) have been described in only three cases (patient ORL, McCarthy & Warrington, 1984; patient EDE, Berndt et al., 1991; and patient JNR, Berthier et al., 2011). Below, a brief summary of the main findings from patient EDE are described. A further description of the other two cases is not provided here because their personal and developmental histories (mixed handedness and perinatal left hemisphere injury in JNR and left-handedness in ORL) invalidate the diagnosis of crossed aphasia.

Berndt et al. (1991) described the case of a 56-year-old, strongly right-handed, housewife (EDE), who acutely developed fluent aphasia with impaired auditory comprehension and rapid cycling mood changes in association with a right posterior cortical infarction. A formal evaluation of deficits in EDE was initiated 10 months after the stroke and by that time her reading and writing deficits had improved more than repetition span and auditory sentence comprehension. Since then language and cognitive deficits remained stable and were longitudinally evaluated during the next five years. An MRI performed approximately four-years post-onset revealed a right temporal-parietal infarction compromising cortical regions (middle temporal gyrus and posterior superior temporal gyrus, temporal pole, and posterior insula) engaged in auditory comprehension. In retrospect, it could be argued that EDE probably had an acute Wernicke's aphasia which gradually resolved to CA in the chronic period (1-year post-onset) (Berndt et al., 1991). Berndt and colleagues interpreted the clinical-anatomical relationships observed in EDE as indicative of "mirror image" crossed CA (Alexander et al., 1989a; Alexander and Annett, 1996; Alexander, 1997), although her performance in repetition and short-term memory tasks was atypical in comparison with other patients presenting with short-term memory deficits after left hemisphere damage. Indeed, EDE had intact input phonological processing, one-item recency effect on list repetition, and absent meaning-based paraphrases during sentence repetition that in the authors' view reflected an atypical interaction between right and left hemispheres (Berndt et al., 1991). Berndt and her colleagues concluded that in EDE: "...there appears to be an unusual dissociation of functions such that the perception of auditory/phonetic information is separated from its storage, while access to semantic information from phonemic forms in connected speech is impaired... some initial processing of auditory/phonetic information is carried out in EDE’s intact left hemisphere, while language functions responsible for phonetic storage and lexical/semantic assignment to sentence constituents are lateralized to the right hemisphere” (p. 277).

Analysis of repetition performance in the other two patients yielded mixed results. Evaluation in patient JNR replicated the results obtained in EDE (except for abnormal phonological input processing), but patient ORL had repetition deficits similar to the ones described in cases with CA and left hemisphere involvement (see further details in Berthier et al., 2011; McCarthy & Warrington, 1984). In light of the limited data available and mixed results on the pattern of repetition in patients with crossed CA, analysis of further cases is clearly needed. In this study, we specifically investigated repetition deficits in a chronic stroke patient with crossed subcortical CA. We also examined for the first time the role of right white matter pathways involvement in repetition processes in crossed aphasia. Our results replicate findings from previous similar cases (Berndt et al., 1991; Berthier et al., 2011) showing that repetition deficits have atypical features in more demanding tasks (sentence repetition) reflecting limited reliance on lexical-semantic processing as has been reported in typical CA associated to left hemisphere damage. Further, our neuroimaging findings suggest that subcortical lesions in the right hemisphere lesioning perisylvian and commissural pathways may account for the observed language deficits by altering the interaction between right and left hemispheres.

Methods & Results - Study 2

PARTICIPANT

We examined language deficits including repetition performance (digits, words/non-words, lists of word pairs and triplets, sentences and novel sentences/idiomatic clichés) in a monolingual Spanish speaking patient with chronic CA secondary to large right hemisphere stroke lesion.

PATIENT JAM

JAM was a 46-year-old man who suffered a large intracerebral haemorrhage in the right striatal/capsular region 1 year before referral to our unit. In the acute period, he had a dense left hemiplegia, left hemianopia, left hemisensory loss, and mild left hemispatial neglect. After a short-lived period of global aphasia, language testing revealed fluent jargon aphasia with impaired auditory comprehension which gradually regressed to CA. Reading and writing were severely affected with features of both deep dysgraphia and deep dyslexia. He also had mild dyscalculia but he did not show ideomotor or buccofacial apraxia as reflected by ceiling scores on the apraxia subtest (60/60) of the WAB (Kertesz, 1982). This later finding is at variance to that commonly observed in patients with CA associated to left hemisphere damage (Geschwind, 1965; Benson et al., 1973; Tognola & Vignolo, 1980). At the time of formal language evaluation JAM was fully oriented and showed adequate insight into his deficits. His affect was flat and he tended to be isolated at home. He met diagnostic criteria for major depression as has been reported in patients with left basal ganglia strokes (Starkstein et al., 1988). JAM was strongly right-handed without history of perinatal injury, developmental delay, or familiar left-handedness. On the

Edinburgh Handedness Inventory (Oldfield, 1971) his score was +100. During the first six months after the stroke, JAM received conventional speech-language therapy on an individual basis (2 h/week) showing improvement in spontaneous speech and auditory comprehension. No beneficial changes were reported on repetition deficits.

IMAGING

METHODS

The MRI study in JAM was per- formed on a 3-T magnet (Philips Gyroscan Intera, Best, The Netherlands) equipped with an eight-channel Philips SENSE head coil. Head movements were minimized using head pads and a forehead strap. High-resolution T1-weighted structural images of the whole brain were acquired with three dimensional (3D) magnetization prepared rapid acquisition gradient echo (3 D MPRAGE) sequence (acquisition matrix: 240/256 r; field of view: 240 ms; repetition time [TR]: 9.9 ms; echo time [TE]: 4.6 ms; flip angle: 8; turbo field echo (TFE) factor: 200; 1 × 1 × 1 mm3 resolution). One hundred eighty-two contiguous slices, each 1-mm thick, 0 mm slice gap, were acquired. The total acquisition time of the sequence was about 4:24 min. In addition to the 3D MPRAGE, a standard axial T-2 weighted/FLAIR (TR = 11.000ms; TE = 125/27 ms; 264 × 512 matrix; field of view [FOV] = 230 × 230; 3-mm-thick slices with 1 mm slice gap) was obtained. A Short TI Inversion Recovery (STIR) was used to produce 24, 2.5 mm axial slices (interslice gap = 1 mm; TR = 4718 ms; TE = 80 ms; inversion time = 200 ms; 264 × 512 matrix; FOV = 230 mm; number of excitations = 2). In JAM the anterior commissure (AC) was identified in axial and coronal T1-weighted images at the level of the temporal stems (Warren et al., 2009).

RESULTS

Axial MRI showed right basal ganglia lesions including the putamen, part of the external pallidum, and anterior limb, genu, and posterior limbs of the internal capsulae extending superiorly to the periventricular white matter (corona radiata). Tissue damage was also present in the white matter surrounding the hippocampus and the middle temporal gyrus with posterior extension to the auditory and optic radiations in the temporal stem (Figure 3). The right posterior ventral and dorsal insular cortices and the periventricular white matter deep to the supramarginal gyrus were also damaged. No lesions were documented in the left hemisphere.

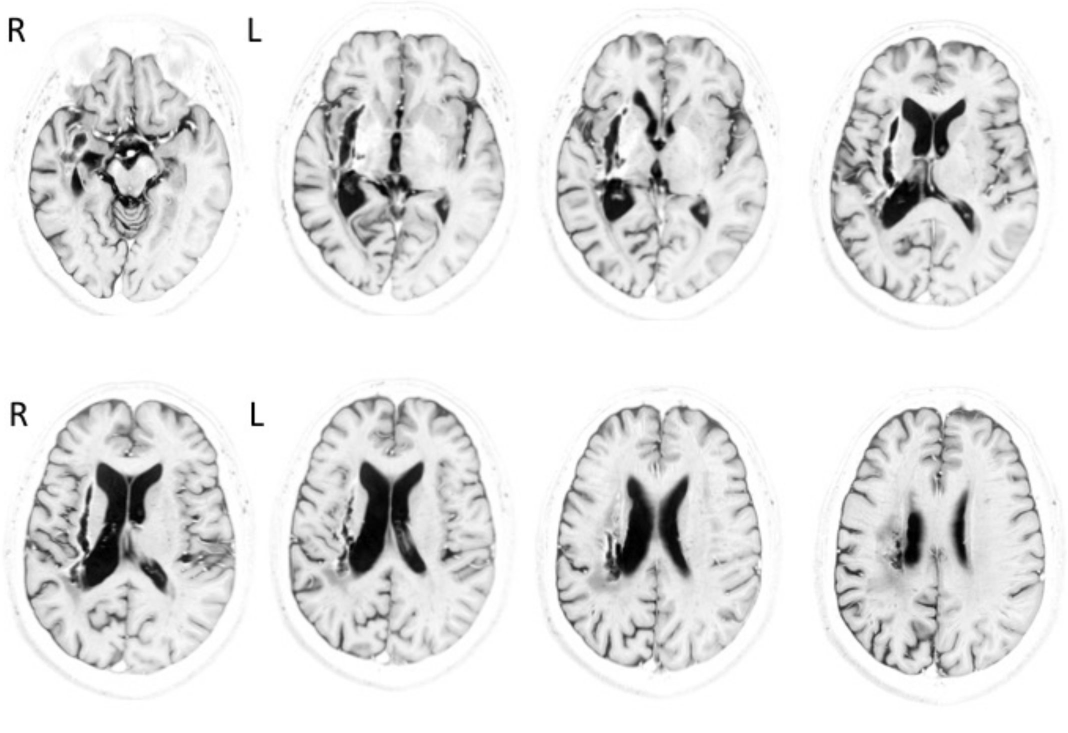

Figure 3. Structural axial MRI of patient JAM showing the full extension of lesions. A 3T MRI (Short T1 Inversion Recovery—STIR—sequence) in JAM show lesion topographies involving the right striatocapsular region with inferior extension to the temporal stem, ventral insular cortex, and inferior fronto-occipital fasciculus. Note superior extension of the lesions to the AF and white matter underneath the supramarginal gyrus.

DIFFUSION TENSOR IMAGING

DTI allows for “in vivo” measurement of the diffusive properties of water in a way that allows information to be garnered about the microstructural organization of tissue (Basser et al., 1994). Tractography enables the orientation of white matter (WM) to be ascertained, thus making possible the segregation of WM into separate sections based on the paths of the distinct tracts (LeBihan, 2003). Data acquisition was performed using multi-slice single-shot spin-echo echo-planar imaging (EPI) with specific parameters as follows: FOV 224 mm, 2-mm-thick slices with 0mm slice gap, TE = 117ms, TR = 12408ms, and b factor: 3000 s/mm2. The EPI echo train length consisted of 59 actual echoes reconstructed in a 112 × 128 image matrix. Sixty-four diffusion directions were used in order to allow for precise construction of the diffusion tensor. Motion and eddy current correction were performed using FSL’s FDT (http://www.fmrib.ox.ac. uk/fsl/) eddy current correction tool (Smith et al., 2004; Woolrich et al., 2009). Diffusion tensor estimation was carried out in using Diffusion Toolkit’s least-square estimation algorithm for each voxel (Ruopeng Wang, Van J. Wedeen, TrackVis.org, Martinos Center for Biomedical Imaging, Massachusetts General Hospital). The whole brain tractography used an angular threshold of 35 degrees and an FA threshold of 0.2. The tensor was spectrally decomposed in order to obtain its eigenvalues and eigenvectors. The fiber direction is assumed to correspond to the principal eigenvector (the eigenvector with the largest eigenvalue). This vector was color coded (green for anterior-posterior, blue for superior-inferior and red for left-right) in order to help generate the color FA map. An FA map was also generated from these eigen values. It was done using Diffusion Toolkit. Virtual dissections of the three parts of the AF and the IFOF were performed by using a region of interest (ROI) approach, following the directions of a white matter tractography atlas (Catani & Thiebaut de Schotten, 2012). All virtual dissections were performed using TrackVis (Ruopeng Wang, and Van J. Wedeen, TrackVis.org, Martinos Center for Biomedical Imaging, Massachusetts General Hospital).

RESULTS

DTI was performed in patient JAM (Figure 4). DTI showed damage to the right long direct segment of the AF and IFOF with relative sparing of the anterior indirect and posterior segments of the AF together with fully developed left AF and IFOF.

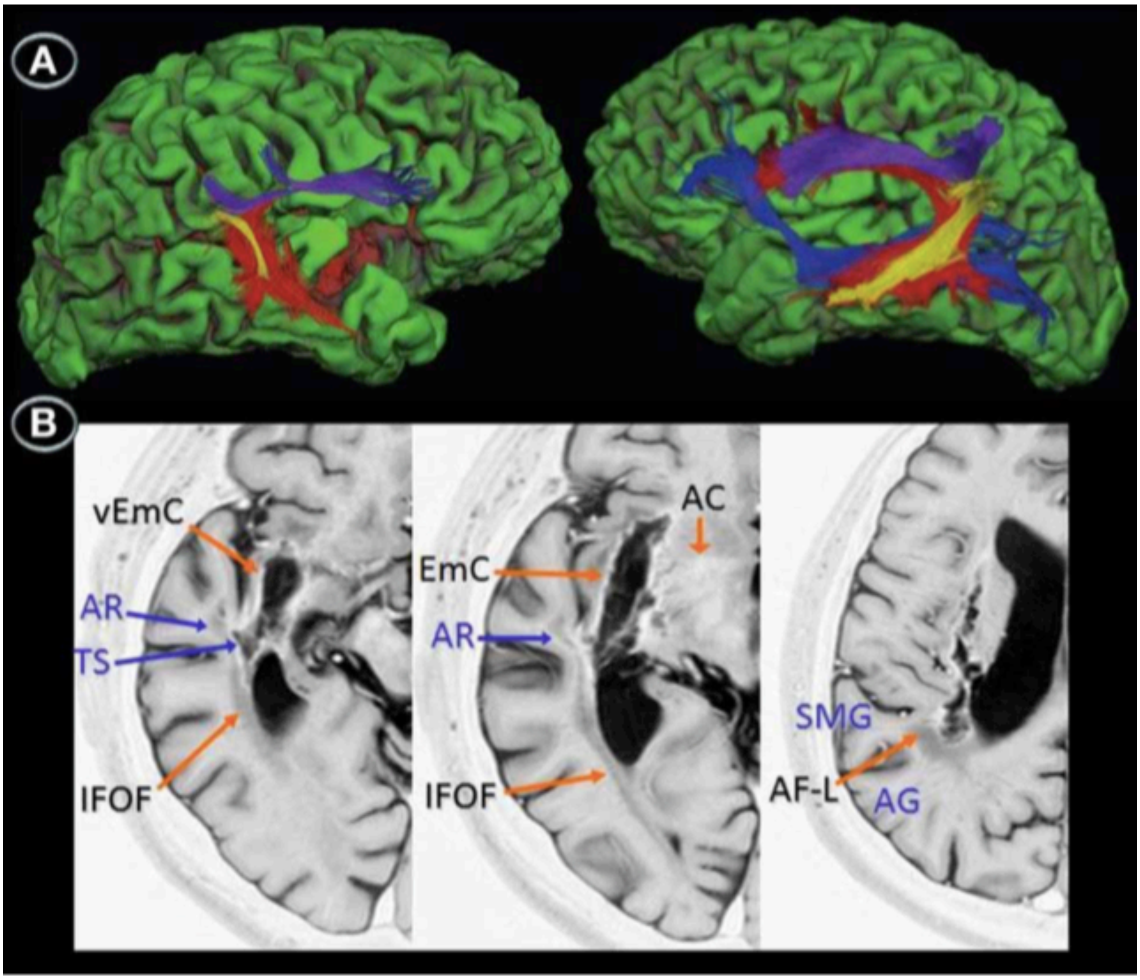

Figure 4. Diffusion tensor imaging (3T MRI) of patient JAM. (A) Uninflated surface of the cerebral hemispheres (FreeSurfer reconstruction) depicting gyri in green and sulci in red. The right image shows a small cortical component of the haemorrhage (red) involving the right anterior insula and superior temporal gyrus. The DTI reconstruction of the AF and inferior fronto-occipital fasciculus shows (left image) damage to the right long direct segment of the AF (red) and inferior fronto-occipital fasciculus (blue) with relative sparing of short and long fibers of the anterior indirect segment (purple) and posterior segments (yellow), whereas the right image shows fully developed left perisylvian white matter pathways. (B) Anatomical axial MRI section (Short T1 Inversion Recovery—STIR—sequence) show the right striatocapsular lesion and perinecrotic tissue with degeneration of several white matter tracts (orange and blue arrows). AR indicates, auditory radiations; TS, temporal stem; SMG, supramarginal gyrus; AG, angular gyrus; EmC, extreme capsulae; vEmC, extreme capsulae; IFOF, inferior fronto-occipital fasciculus; AC, anterior commissure; AF-L, arcuate fasciculus-long segment

LANGUAGE ASSESSMENT

JAM had an Aphasia Quotient of 79.6 (mild to moderate aphasia). JAM showed a combination of fluent and well-articulated spontaneous speech with rare phonemic paraphasias and occasional approximation to target words to repair errors (conduite d'approche), preserved auditory comprehension except for sequential commands and impaired repetition of multisyllabic words and sentences. Naming was relatively preserved. His WAB scores (fluency: 9, comprehension: 7.4, repetition: 6.2, naming: 9.2) were consistent with the diagnosis of CA (Kertesz, 1982).

EXPERIMENTAL ASSESSMENTS

To explore the interaction between phonology and lexical-semantic processing, JAM was evaluated using selected subtests from the PALPA (Kay et al., 1992; Valle & Cuetos, 1995; Kay & Terry, 2004) and a battery of experimental tests (Berthier, 2001).

PHONOLOGICAL PROCESSING

WORD PAIR DISCRIMINATION

METHODS

Four PALPA subtests were used to evaluate auditory processing for discriminating minimal pairs. These included Non-word Minimal Pairs (PALPA 1), Word Minimal Pairs (PALPA 2), Word Minimal Pairs Requiring Written Selection (PALPA 3), and Word Minimal Pairs Requiring Picture Selection (PALPA 4). The minimal pairs tests from the PALPA required same/different judgments for pairs of monosyllabic words/non-words that differed by a single phonetic feature (e.g., "sol-col" [sun-cabbage]). In half the trials, the two stimuli were identical and in half they were different.

RESULTS

JAM had abnormal performance on auditory discrimination of non-word minimal pairs with significantly better performance on same pairs relative to different pairs which resulted from his tendency to classify most pairs as similar [$\chi 2(1) = 25.2$, $p < 0.0001$]. Performance was significantly better discriminating identical minimal word pairs than different word pairs in both JAM [$\chi 2(1) = 9.68$, $p = 0.002$]. Scores in word minimal pairs requiring picture selection were relatively preserved in JAM (Table 4).

RHYME JUDGMENTS

METHODS

Three PALPA subtests were used to evaluate processing for Rhyme Judgments in Auditory/Written (PALPA 15) and Pictures (PALPA 14) presentations. In each rhyme judgment task, two words were presented in the corresponding modality and the patient was required to say whether or not they rhymed (e.g., “tarta-carta” [cake-letter]). There were 40 trials divided equally between rhyming and non-rhyming pairs.

RESULTS

The ability of JAM to make rhyme judgments was abnormal in all modalities of presentation (auditory and written words and pictures) (Table 4).

Table 4| Phonological processing

Test	JAM	Normative Data**
Nonword Minimal Pairs (test 1)		
Same	28/28 (1.00)*	27.45 ± 0.99
Different	9/28 (.32)	27.09 ± 1.24
Word Minimal Pairs (test 2)		
Same	28/28 (1.00)	27.54 ± 1.27
Different	18/28 (.64)	27.68 ± 0.76
Word Minimal Pairs Requiring Picture Selection (test 4)	38/40 (.95)	38.95 ± 1.66
Rhyme Judgements Words (test 15)	23/40 (.58)	35.05 ± 2.79
Rhyme Judgements Pictures (test 14)	24/40 (.60)	33.59 ± 3.49
Rhyme Judgements Written Version (test 15)	23/40 (.58)	35.05 ± 2.79
Auditory Lexical Decision (test 5)		
High imageability-high frequency	20/20 (1.00)	20.00 ± 0.00
High imageability-low frequency	20/20 (1.00)	20.00 ± 0.00
Low imageability-high frequency	20/20 (1.00)	19.95 ± 0.21
Low imageability-low frequency	17/20 (.85)	19.41 ± 1.15
Nonwords	75/80 (.94)	78.18 ± 1.95
Visual Lexical Decision (test 25)		
High imageability-high frequency	20/20 (1.00)	20.00 ± 0.00
High imageability-low frequency	18/20 (0.90)	20.00 ± 0.00
Low imageability-high frequency	20/20 (1.00)	19.95 ± 0.21
Low imageability-low frequency	20/20 (1.00)	19.41 ± 1.15
Nonwords	67/80 (.84)	78.18 ± 1.95
Single Word Comprehension		
Spoken word-picture matching (test 47)	37/40 (.93)	39.45 ± 1.67
Written word-picture matching (test 48)	39/40 (.98)	39.64 ± 1.46
Sentence Comprehension		
Auditory sentence comprehension (test 55)	32/60 (.53)	58.25 ± 2.61
Written sentence comprehension (test 56)	41/60 (.68)	57.73 ± 2.60

γγTest number follows the nomenclature of the original English version of PALPA (*see* Kay and Terry, 2004) which is sligthly different from the Spanish version. *Numbers in parentheses indicate proportion of correct responses. **Normative data from Valle and Cuetos (1995). Written lexical decision (missed data).

LEXICAL PROCESSING

LEXICAL DECISION

METHODS

Word/non-word discrimination was assessed with the Auditory Lexical Decision: Imageability × Frequency (PALPA 5) and the Visual Lexical Decision: Imageability and Frequency (PALPA 25). These two versions were administered 2 weeks apart to prevent learning. These tests use 80 words of high- and low-imagery and high- and low- frequency and 80 non-words derived from each of the real words by changing one or more letters. All non-words follow Spanish spelling rules and were pronounceable (Valle & Cuetos, 1995).

RESULTS

JAM performance on Auditory Lexical Decision was preserved for words (77/80) and non-words (75/80) [$\chi2(1) = 0.13$, $p = 0.718$]. Misses occurred in three low-imageability/low-frequency items (“anger,” “dogma,” “satire”), whereas false alarms in non-words were derived from low- imageability words (Table 4). On Visual Lexical Decision JAM had better recognition of words (78/80) than non-words (67/80) [$\chi2(1) = 7.31$, $p = 0.007$].

SINGLE WORD COMPREHENSION

METHODS

Single word comprehension was assessed with the Spoken Word—Picture Matching (PALPA 47) and the Written Word— Picture Matching (PALPA 48) tasks. The two versions were administered 2 weeks apart to prevent learning.

These tasks required that the patient match a spoken or a written closely semantic, one distantly semantic; one visual, and one unrelated.

RESULTS

The performance of JAM was relatively preserved on the auditory and written presentations (Table 4).

SENTENCE COMPREHENSION

METHODS

Sentence comprehension was assessed using the Auditory Sentence Comprehension (PALPA 55) and the Written Sentence Comprehension (PALPA 56) tasks. These two versions were administered 2 weeks apart to prevent learning. These tasks require matching an auditory or written sentence presented with one of three figures, the target one and two distractors. Several types of sentences were examined including reversible (e.g., “The dog is approaching the girl”) and non-reversible (e.g., “The dog is washed by the girl”) sentences, active and passive sentences, directional and non-directional sentences, and gapped sentences.

RESULTS

JAM showed severely impaired performance in both auditory and written modalities of presentation. Their performance was similar for reversible and non-reversible sentences (Table 4).

REPETITION OF WORDS AND NON-WORDS

METHODS

Length, frequency, and imageability of words can influence the accuracy of repetition amongst aphasic patients. Studies in CA suggest that repetition of short words is better than repetition of multisyllabic and grammatical words (Goodglass, 1992; Nadeau, 2001). Therefore, performance on output phonological tasks was assessed with two repetition subtests [Repetition: Syllable Length (PALPA 7) and Repetition: Non-words (PALPA 8)]. These tests contain 24 words and 24 non-words of increased length (three–six letters). To further evaluate potential dissociations in repetition performance between words and non-words, the Repetition: Imageability × Frequency (PALPA 9) subtest was also administered. This test contains 80 words and 80 non-words presented in a mixed fashion. Words were grouped in four lists (20 items in each list) with variations in frequency and imageability. The lists contained high-frequency/high-imageability, high-frequency/low-imageability, low-frequency/high-imageability, and low-frequency/low-imageability words. These lists were matched for syllable length; items contained between one and four syllables. The non-words were matched to the words for phonological complexity. Errors in all repetition tasks were analyzed by two of us (ID-T, GD).

RESULTS

Word repetition (PALPA 7) was mildly impaired in JAM (0.88). Scores in word repetition were marginally better than those found in non-words (PALPA 8) in JAM [$\chi 2(1) = 3.72$, $p < 0.054$]. In PALPA 9, no differences were found in JAM [$\chi 2(1) = 1.51$, $p = 0.22$].

DIGIT PRODUCTION AND MATCHING SPAN

METHODS

This was assessed with the Digit Production/Matching Span (PALPA 13).

RESULTS

JAM has restricted digit production and matching span (Table 5) word to one of five pictures (target nouns and four distractor items [one p = 0.014]. Regarding word repetition in PALPA 9 test, he repeated items of the four lists with relatively similar efficiency. Repetition of low-imageability and low- frequency words in JAM (0.70). It should be noted that most non-words in the Spanish version of the PALPA 9 (Valle & Cuetos, 1995) have high word-likeness (Gathercole & Marin, 1996) because they are derived from words with a single consonant (n = 30; “pierna” [leg] → pierla) or a vowel [n = 22; “hospital” (hospital) → hospitel] exchanged. While word-likeness increases the likelihood of lexicalization on repetition tasks in patients with typical CA and left hemisphere damage (Saito et al., 2003), this was not the case in our patient as lexicalizations during non-word repetition (PALPA 9) were rare (4/80 [0.05]).

Table 5| Auditory Processing: Repetition of Digits, Single Words and Nonwords

Test	**JAM**	**Normative data****
Digit Production/Matching Span	2/3	5.91 ± 0.67 / 6.18 ± 1.34
Words (test 7)[γ]	21/24 (.88)	23.81 ± 0.23
Nonwords(test 8)	14/24(.58)	22.95 ± 0.63
Imageability x Frequency (test 9)		
Words	46/80 (.57)	
Nonwords	79/80 (.98)	
Grammatical Class (test 10)		
Nouns	13/20(.65)	20.00 ± 0.00
Adjectives	12/20(.60)	19.95 ± 0.21
Verbs	12/20(.60)	19.91 ± 0.29
Functors	12/20(.60)	19.82 ± 0.49
Morphology (test 11)		
Regulars and control of regulars	11/20(.55)	19.83 ± 0.63
Irregulars and control of irregulars	18/20 (.90)	19.86 ± 0.25
Derivates and control of derivates	13/20(.65)	19.81 ± 0.27

[γ] Test 7 *versus* test 8: $\chi^2_{(1)}$: 12.2, $p < 0.001$. *Numbers in parentheses indicate proportion of correct responses.
**Normative data from Valle and Cuetos (1995).

REPETITION: GRAMMATICAL CLASS AND MORPHOLOGY

METHODS

Grammatical class (PALPA 10) and morphological endings (PALPA 11) were evaluated in JAM. PALPA 10 evaluates the effect of grammatical class. This test contains 80 words grouped in four different categories (nouns, adjectives, verbs, and functors) of 20 items in each list. PALPA 11 evaluates whether repetition is affected by morphological endings. This test contains 60 words grouped in three lists (regulars and control of regulars, irregulars and control of irregulars and derivates and control of derivates).

RESULTS

Scores in PALPA 10 ranged from mildly (0.80) to moderately (0.60) impaired in JAM, but repetition performance was not influenced by grammatical class. Repetition with different morphological endings in JAM had low average (0.90) repetition of irregulars and controls of irregulars and moderately impaired (0.60) regular and derivates and their controls (Table 5).

WORD PAIR REPETITION

METHODS

To assess the influence of lexical-semantic information on repetition ability when the demand of the auditory-verbal short- term memory is increased, he was asked to repeat word pairs (e.g., “house-flower”) (n = 56). The patient was asked to repeat immediately after auditory presentation in a no-delay direct condition (Martin et al., 1996; Gold & Kertesz, 2001) a total of 112 high-frequency words. The total list was composed of high-frequency/high imageability (n = 28), high-frequency/low-imageability (n = 28); low-frequency/high-imageability (n = 28) and low-frequency/low-imageability (n = 28) words. Responses were scored for the number of word pairs repeated verbatim and for the number of words repeated accurately as a function of serial position (initial and final) in the list, irrespective of whether the word pair was repeated accurately or not. The number of correct words, failures to respond, and semantic, phonologic, formal, neologistic, perseverative, and unrelated lexical errors was evaluated.

RESULTS

Performance on this task was moderately impaired in him. Table 6 shows the number of word pairs that were repeated correctly. Further analyses disclosed that JAM repeated correctly 74 of the total 112 (0.66) words. There was a serial position effect (initial = 43/56; terminal = 26/56) [χ2(1) = 9.58, p = 0.002] which may be attributable to his markedly reduced memory span (two items). There were no effects of frequency/imageability. Abnormal responses were ordered by the frequency of occurrence and included: failures to respond = 17 (0.44), phonological errors = 7 (0.19), neologisms = 5 (0.14), formal errors = 4 (0.11), unrelated errors = 4 (0.11), and perseverations = 1 (0.2). There were no semantic errors. There were no serial position effects (initial = 30/56; terminal = 29/56) on word pair repetition which may be attributable to her memory span (three items). Her responses included phonological errors = 22 (0.49), neologisms = 11 (0.24), formal errors = 7 (0.16), failures to respond = 3 (0.07), unrelated errors = 1 (0.02), and perseverations = 1 (0.2). There were no semantic errors.

Table 6| Auditory Processing: Repetition of Three-Word Lists and Sentences

Test	JAM	Normative data**
High Frequency	Words _ Triplets	
Random	1/30 (.00) _ 0/10 (0.0) ***	19.0 ± 0.8 (range: 17-20)
Loosely constrained	0/30 (.00) _ 0/10 (0.0) ***	18.7 ± 1.0 (range: 17-20)
Constrained	26/60 (.43) _ 0/20 (0.0) ***	19.4 ± 0.6 (range: 18-20)
Total	27/120 (.23) _ 0/40 (0.0) ***	
Low Frequency		
Random	0/30 (.00) _ 0/10 (.00) ***	17.0 ± 2.5 (range: 11-20)
Loosely constrained	0/30 (.00) _ 0/10 (.00) ***	18.6 ± 1.3 (range: 16-20)
Constrained	6/30 (.20) _ 0/10 (.00) ***	18.7 ± 1.2 (range: 16-20)
Total	6/90 (.06) _ 0/30 (.00) ***	
Sentences (test 12)	2/36 (.05) ***	Not tested
Idiomatic phrases*	8/40 (.20) ***	Not tested
Novel phrases*	9/40 (.20) ***	Not tested

* numbers in parentheses indicate proportion of correct responses unless indicated. ** taken from Berthier (2001).
***Abnormal results

REPETITION OF WORD TRIPLETS

METHODS

JAM was also asked to repeat word triplets. This task is a modification of the one used by McCarthy and Warrington (1984, 1987) in patients with CA. In the present battery two sets of 60 three-word lists (verb-adjective-noun) were created (Berthier, 2001). These were composed of word strings of increasing semantic richness that is from non-organized to organized semantic information. Two three-word lists of 20 items each (List 1: 60 high- frequency words; List 4: 60 low-frequency words) consisted of random word combinations (e.g., "buy-sweet-country"). Two other 20 three-words lists (List 2: 60 high-frequency words; List 5: 60 low-frequency words) conveyed loosely constrained meaningful information (e.g., "defend-hero-gold”), and two other 20 three-word lists (List 3: 60 high-frequency words; List 6: 60 low-frequency words) conveyed closely constrained meaningful information (e.g., “cut-lovely-flower”). Words were read at a rate of one per second and JAM was required to repeat the words in the order given by the examiner. Responses were scored for the number of lists repeated verbatim in each condition and for the number of words repeated accurately as a function of serial position (initial, medial and final) in the list, irrespective of whether the whole triplet was repeated accurately or not. The number of correct words, failures to respond, and semantic, phonologic, formal, neologistic, perseverative, and unrelated lexical errors was evaluated.

RESULTS

Performance on this task was severely impaired in him (Table 6). JAM failed to repeat any word triplet correctly (e.g., “read-new-book” → read . . . don’t know). Since he became frustrated after repeated unsuccessful attempts the task was discontinued after 10 consecutive failures in each list. Analysis of individual words during these interrupted trials indicated that JAM repeated more words in triplets rich in semantic relations than in the other lists, showing significantly better performances in high-frequency triplets than low-frequency triplets [$\chi2(1) = 4.17$, $p < 0.041$].

Note that since in JAM this task was interrupted after 10 consecutive failures in each list, only 180 words could be analyzed. His responses were failures to respond = 144 (0.80), semantic errors = 5 (0.03), perseverations = 4 (0.02), phonological errors = 3 (0.02), unrelated errors = 2 (0.01), and neologisms = 1 (0.00). Patient’s performance according to the serial position in the list were relatively similar for initial (0.3), medial (0.1), and terminal (0.7) positions.

REPETITION OF SENTENCES

METHODS

Sentence repetition was assessed with the PALPA 12. This task evaluates the ability to repeat auditorily-presented sentences (n = 36) of different length (from 5 to 9 words). It is composed of reversible sentences (n = 20) and non-reversible (n = 16) sentences. Serial position curves were generated for all 7-word sentences (n = 18).

RESULTS

Sentence Repetition (PALPA 12) was severely abnormal in him (Table 6). JAM could repeat some non-reversible sentences yet his performance was severely abnormal (8/36 [.22]). Error analysis revealed that he omitted many words and mainly produced phonological errors. JAM produced rare semantic errors ("man" → owner) and semantic perseverations. There were no paraphrases in strict sense, except for the presence of a difficult to classify sentence (sentence 17: "This dog has more cats to chase" → This dog . . . this cat, there are more to run) in which the meaning of the original sentence was not fully replicated in the response (Saffran & Marin, 1975). Analyses of serial position curves of seven word sentences revealed a tendency for repeating initial (items one and two) and terminal (item 6) words (range of correct for these positions: 60–80%) correctly with frequent omissions (range of correct: 20–40%) of words in the midportion of sentences (items three, four, five) in JAM.

REPETITION OF CLICHÉS AND NOVEL SENTENCES.

METHODS

To explore possible dissociation between both types of sentences, JAM was asked to repeat familiar idiomatic Spanish sentences (clichés) (n = 40) taken from the 150 Famous Clichés of Spanish Language (Junceda, 1981) as well as a set of novel sentences (n = 40) that were construed following the methodology described by Cum and Ellis (1999) and Berthier et al. (2011). For example, for the idiomatic cliché: “Me lo dijo un pajarito” (“A little bird told me”) the novel control sentence: “Me lo dijo mi compadre” (“My friend told me”) was created.

RESULTS

JAM was moderately impaired in these tasks obtaining relatively similar scores in both types of sentences. He rarely made paraphrases in novel sentence repetition (3/40 [.08]) and only 1 paraphrase (1/40 [.02]) was heard in repetition of idiomatic clichés (“Mess things up” → Make a mess).

Discussion - Study 2

We have described the profile of language deficits in a chronic aphasic patient. They did poorly in input phonological tasks (minimal pairs, rhyme judgments) when stimuli were presented in auditory and written modalities. Lexical-semantic processing for single words (lexical decision, comprehension) was relatively preserved in these input modalities, but JAM infrequently accessed meaning when asked to comprehend and repeat complex verbal messages. Indeed, a relatively preserved performance in single word repetition contrasted with a severe impairment in repetition of digits, non-words, word lists, sentences, novel phrases and idiomatic clichés. In several instances, repetition was not significantly influenced by the frequency, imageability, and lexicality of stimuli. This atypical combination of language deficits could also be deemed uncommon because they took place in a strongly right-handed patient with residual crossed CA associated with predominantly right striatal/capsular lesions also affecting the AF, IFOF, anterior commissure, and temporal stem. The distinctive features of this clinical-anatomical correlation are discussed below.

CROSSED SUBCORTICAL APHASIA

Crossed subcortical aphasia is a rare condition to the extent that in a recent review of the literature only nine cases met criteria for “possibly reliable” or “reliable” diagnosis (De Witte et al., 2008). During the acute and early chronic periods JAM most likely had Wernicke’s aphasia and left hemiplegia which resulted from extensive right striatal/capsular lesions extending into the temporal stem/IFOF and supramarginal gyrus/AF. This clinical-anatomical correlation likely represents the right-sided analogue to the syndrome of Wernicke-type aphasia with right hemiparesis secondary to left subcortical injury originally described by Naeser et al. (1982). This syndrome, which is considered a rare entity (Wolfe & Ross, 1987), usually occurring with atypical language deficits (Damasio et al., 1982), has not been well-defined in crossed aphasic patients (Basso et al., 1985). In their original publication, Naeser and colleagues (1982) described three aphasic syndromes associated with left capsular/putaminal involvement and variable lesion extension to either anterior-superior, posterior, or both anterior-superior and posterior neighboring structures. Of these, the syndrome that best fits with the one we found in JAM after right hemisphere injury is characterized by poor comprehension, fluent Wernicke's type speech, and lasting right hemiplegia in association with left capsular/putaminal damage and posterior lesion extension to the auditory radiations in the temporal stem (Cases 4, 5, and 6 in Naeser et al., 1982, pp. 8-10). In Naeser et al.'s case series (1982) testing in the chronic period was possible in one patient and it revealed improvement in all language modalities.

Our patient may be interpreted as presenting "mirror image" crossed CA (Alexander et al., 1989a) for two reasons: (1) similar surface symptoms and lesion topography to the syndrome described after left hemisphere involvement; and (2) gradual resolution of language deficits from receptive aphasia to a less severe CA as is regularly described in cases with Wernicke's aphasia and left hemisphere lesions (Goodglass, 1992). Regrettably, in the aphasic patients with left "capsular/putaminal with posterior lesion extension" described by Naeser et al., 1982 language deficits (including repetition) were succinctly described, thus making it hard to establish whether or not their intrinsic characteristics were typical. Increasing our understanding on this issue is desirable because evaluation of repetition deficits in patients with “mirror image” crossed CA has been performed only in patient EDE who unexpectedly showed atypical performance on word list and sentence repetition (Berndt et al., 1991). This would mean that repetition deficits in some cases with right-hemisphere language dominance deviate from the classical pattern reported in similar cases with left hemisphere dominance because the neural organization of language in the former is different. Regrettably, the scarcity of similar well-studied cases and the reported heterogeneity in demographic and clinical-anatomic variables prevent further elaborations. It suffices to say that atypical neural organization of language in the right hemisphere may apply for patient EDE with right temporal-parietal involvement (Berndt et al., 1991) but possibly not for ORF, a left-handed conduction aphasic patient with right parietal damage and good access to meaning during word list and sentence repetition (McCarthy & Warrington, 1984).

It is even more difficult clarifying the finding of atypical language deficits in our crossed aphasic patient with striatal/capsular involvement because atypical language deficits are common in left subcortical aphasia (Albert et al., 1981; Damasio et al., 1982; Fromm et al., 1985) and because the role of left basal ganglia in language deficits is still controversial (Damasio et al., 1982; Naeser et al., 1982; Cappa et al., 1983; Nadeau & Crosson, 1997). Most studies evaluating subcortical stroke provided evidence against a prominent role of basal ganglia in language and instead attributed language deficits to the deleterious effect of subcortical involvement on the overlying cortex (Nadeau & Crosson, 1997; Hillis et al., 2002; Radanovic & Scaff, 2003; de Boissezon et al., 2005; Choi et al., 2007). One study on vascular aphasia secondary to left subcortical lesions mainly affecting the striatum ascribed lexical-semantic deficits to dysfunction of the basal temporal language area and IFOF (de Boissezon et al., 2005). Anatomical data in our patient with crossed CA also suggest that the pattern of language deficits (impaired sentence comprehension, sentence repetition) may be linked to damage to the right basal temporal language area and white matter tracts rather than to the striatocapsular lesions.

DISSOCIATED STRUCTURE-FUNCTION RELATIONSHIPS IN CROSSED SUBCORTICAL APHASIA?

There is some evidence that the AF is asymmetric being larger in volume and having a higher fiber density in the left hemisphere compared to the right (Parker et al., 2005; Powell et al., 2006; Vernooij et al., 2007; Catani & Mesulam, 2008; Axer et al., 2012; Catani & Thiebaut de Schotten, 2012). Combining DTI and fMRI in a small group of strongly right-handed healthy subjects, Powell et al. (2006) demonstrated for the first time that a greater development of left hemisphere white matter tracts in comparison with their homologues counterparts correlated with left-sided lateralization of language function. Although this structure-function correspondence has been replicated in subsequent studies (Matsumoto et al., 2008; Saur et al., 2008), other studies variously combining DTI with fMRI, Wada test, or other ancillary methods (resting-state functional connectivity analysis) have questioned the long-held assumption that leftward asymmetry in volume of cortical areas (planum temporale) and white matter pathways underlie functional lateralization (see references in Vernooij et al., 2007; Turken & Dronkers, 2011). In complimentary terms, differences in the intra- and inter-hemispheric architecture and function of perisylvian white matter tracts exist and might account for the distinct performance in verbal repetition in healthy subjects (Catani et al., 2007) and in patients presenting with contrasting aphasic deficits

(CA versus transcortical aphasias) (Catani et al., 2005; Berthier et al., 2012). In fact, DTI studies reveal intra- and inter-hemispheric variability of white matter pathways underpinning repetition, most notably of the AF/ superior longitudinal fasciculus (SLF) (Nucifora et al., 2005; Catani & Mesulam, 2008; Gharabaghi et al., 2009; Friederici & Gierhan, 2013). Leftward biased asymmetry of the AF/SLF predominates in males and usually coexists with the absence or vestigial development of its long segment in the right hemisphere (Catani et al., 2005; Powell et al., 2006; Catani & Mesulam, 2008; Thiebaut de Schotten et al., 2011; Catani & Thiebaut de Schotten, 2012; Häberling et al., 2013) although at least one study reproduced the left hemisphere architecture and connectivity in the right hemisphere (Gharabaghi et al., 2009). Another study found reversed asymmetry of the AF in healthy males with right hemisphere language lateralization (Häberling et al., 2013). More symmetric patterns (bilateral-left and bilateral) of the AF/SLF prevail in females (~40%) and some researchers consider that other white matter bundles (IFOF) are also less lateralized than the dorsal stream but this has not been confirmed in all studies (Cao et al., 2003; Rodrigo et al., 2007). Regarding function of the AF/SLF, recent studies using Wada test (Matsumoto et al., 2008) or fMRI (Saur et al., 2008) documented leftward lateralization in subjects with left hemisphere dominance for language; however, it has also been shown that left-handeds with right hemisphere language dominance (as seen using fMRI) (Vernooij et al., 2007) actually have left-lateralized AF. Taken together these later findings align with the hypothesis that lateralized hemispheric function is not always guided by structural asymmetry (Wada, 2009). In support of this view, we did find dissociation between structure and function in JAM. The extensive right subcortical lesion in JAM hindered not only the comparison of inter-hemispheric AF and IFOF architecture but also the possibility of ruling out a reversal of the anatomical asymmetry. Nevertheless, the DTI identified well-developed residual components (anterior indirect and posterior segments) of the right AF/SLF that have escaped from tissue damage together with fully developed AF and IFOF in the left hemisphere which suggest symmetric or leftward lateralization. Despite this structural arrangement, JAM had right hemisphere dominance for language as reflected by his severe and long-lasting repetition disorder consequential to damage to the right AF/SLF and IFOF. Our study did not provide direct evidence of the functional activity of the left white matter tracts (AF, IFOF), yet the persistence of severe deficits on repeating (non-words, word lists and sentences) and accessing meaning during both sentence comprehension and repetition one year after stroke onset makes the natural and therapy-based compensation of such deficits by means of the fully-developed left white matter tracts negligible. Nevertheless, further studies are clearly needed to establish the structure-function relationships amongst individuals with atypical language lateralization.

IS REPETITION ATYPICAL IN CROSSED SUBCORTICAL APHASIA?

In JAM word repetition scores ranged from normal to mild impairment but their performance in non-word repetition was markedly abnormal, a profile generally described in patients with CA and left hemisphere damage (Caplan & Waters, 1992; Goodglass, 1992). Functional neuroimaging in healthy subjects shows activation of superior temporal and premotor cortices bilaterally during single word repetition, whereas non-word repetition activates the same cortical regions mostly in the left hemisphere (Weiller et al., 1995; Saur et al., 2008). Studies combining fMRI with DTI reveal interaction between superior temporal and premotor areas during sublexical repetition via the AF/SLF (Saur et al., 2008). Based on these observations the likely mechanism accounting for the superior performance in JAM on repeating words over non-words may be the conjoint activity of residual areas of the injured right hemisphere and the intact left hemisphere (Weiller et al., 1995; Ohyama et al., 1996; Abo et al., 2004). Poor non-word repetition may be the expected consequence of right hemisphere damage with limited possibility of natural left hemisphere compensation. In support, lesion analysis and DTI findings in JAM showed massive involvement of the long direct segment of the AF normally engaged in auditory/phonological transcoding (word and non-word repetition) (Catani et al., 2005; Saur et al., 2008; Catani & Thiebaut de Schotten, 2012; Cloutman, 2012; Friederici & Gierhan, 2013). It should be noted, however, that their performance in other repetition tasks differed in a number of important respects from typical CA associated with left hemisphere lesions (Saffran & Marin, 1975; McCarthy & Warrington, 1984, 1987; Martin, 1996; Martin & Saffran, 1997; Gold & Kertesz, 2001; Bartha & Benke, 2003). Repetition in phonologically-impaired patients with left hemisphere involvement (e.g., CA) is generally reliant on lexical-semantic processing (McCarthy & Warrington, 1984, 1987; Martin & Saffran, 1997; Jefferies et al., 2007). The use of this alternative strategy increases the likelihood of producing word errors (formal paraphasias) and semantic errors particularly in highly demanding tasks such as immediate serial repetition of word lists and sentences and delayed repetition (Martin et al., 1994; Martin, 1996; Gold & Kertesz, 2001; Jefferies et al., 2006). Additionally, reliance on lexical-semantic processing in some conduction aphasic patients with severely abnormal phonological processing is manifested by “part of speech” effects (e.g., nouns are repeated better than verbs) and production of semantic paraphasias ("necklace" → gold) during single word repetition (deep dysphasia) (Michel & Andreewsky, 1983; Katz & Goodglass, 1990; Butterworth & Warrington, 1995; Martin, 1996; Martin et al., 1996; Ablinger et al., 2007; Jefferies et al., 2007). Such overreliance on lexical-semantic processing allows CA patients to excel in repetition tasks tapping these functions relative to other tasks taxing phonological processing. In this vein, patients with typical CA show better repetition of low- frequency words embedded as the last word in a sentence than when the same word is presented in isolation (McCarthy & Warrington, 1984). Abnormal performance in repeating meaningless word lists by conduction aphasics improves when the meaningfulness of lists is increased (McCarthy & Warrington, 1987) and these patients are also better able to repeat novel sentences which require access to meaning than over-learned idiomatic clichés (McCarthy & Warrington, 1984; Berthier, 1999). Finally, verbatim repetition of word lists and sentences poses serious difficulties to conduction aphasics due to their impaired capacity to hold the phonological trace in AVSTM forcing them to process sentences by meaning and producing paraphrases of the target sentence during repetition (Saffran & Marin, 1975; Martin, 1993; Bartha & Benke, 2003).

Our patient repeated words more accurately than non-words and stimulus length influenced more than frequency/imageability the dissociation between word and non-word repetition. Nevertheless, the occurrence of other above-mentioned features of typical CA did not occur in all repetition tasks in our patient. Indeed, frequency/imageability, and grammatical class had no influence on single word repetition performance, although we acknowledge that in one such task (imageability/frequency) JAM obtained high scores that may have attenuated differences due to ceiling effects. This effect was not observed in JAM in the other task (grammatical class), however. Word pair repetition was moderately impaired. Moreover, the patient produced more omissions and phonological errors than formal errors or word pair repetition and there were no semantic paraphasias, a pattern of performance that differs from the “lexical bias” (formal and semantic errors > phonological errors) reported in patients with typical CA and left hemisphere damage (Gold & Kertesz, 2001). Since word triplet repetition was extremely poor in him, we analyzed the accuracy of individual words on triplets. There was an influence of frequency in JAM who produced more correct items while repeating high-frequency than low-frequency lists. Moreover, he accurately repeated more individual words in triplets containing meaningful semantic information than in other conditions, thus implying that accurate repetition required semantic support. However, reliance on lexical-semantic processes could be deemed incomplete because JAM did not produce meaning-based paraphrases (e.g., “eat-delicious-apple” → eat-juicy-fruit) which is at variance to that frequently reported in patients with typical CA during repetition of two- and three-word lists (Gold & Kertesz, 2001; Berthier et al., 2012). Repetition of sentences from PALPA 12 was severely impaired in JAM and rarely produced ill-formed paraphrases in this task, novel sentences and clichés. Limited lexical-semantic access during word triplet and sentence repetition is in accord with findings from the two previous cases of crossed CA (Berndt et al., 1991; Berthier et al., 2011). Moreover, superior repetition of novel sentences over idiomatic clichés previously reported in typical CA patients (McCarthy & Warrington, 1984) reflecting overreliance on lexical-semantic processes was not observed in JAM. Finally, it should be noted that JAM had more reliance on lexical-semantic processes in other output modalities (reading and spelling) (De-Torres et al., in press), a dissociation already reported in other patients with "deep" disorders (e.g., Miceli et al., 1994; Jefferies et al., 2007). Analysis of further cases is clearly needed to examine whether or not interactions between phonological and lexical-semantic systems in crossed CA are dysfunctional.

If we accept that JAM, and the two previously published cases, EDE (Berndt et al., 1991) and JNR (Berthier et al., 2011) had limited access to meaning at least during sentence comprehension and repetition, the question arising now is which neural mechanisms are dysfunctional. Analysis of available brain images in this case and the outline of white matter tracts with the aid of a fiber tract atlas (Catani & Thiebaut de Schotten, 2012) in JAM and DTI analysis revealed that cortical and subcortical lesions unfailingly compromised the right dorsal (AF) and ventral auditory processing streams (IFOF) in all cases. DTI in JAM disclosed damage to the right long direct segment of the AF and IFOF with relative sparing of the anterior indirect and posterior segments, together with fully developed left AF and IFOF. The role of the dorsal language stream system (AF/SLF) is to monitor auditory-motor integration of speech by allowing a fast and automated preparation of copies of the perceived speech input (Saur et al., 2008; Peschke et al., 2009; Rijntjes et al., 2012). Some components of this long-distance bundle have also been linked to attention and short-term maintenance of phonological traces (Majerus, 2013). The ventral language pathways (inferior longitudinal fasciculus, IFOF and uncinate fasciculus) participate in comprehension by mapping sounds onto meaning (Saur et al., 2008; Peschke et al., 2009; Weiller et al., 2011; Cloutman, 2012) although the precise functional role of every tract is still controversial (Duffau et al., 2009; Harvey et al., 2013). These white matter bundles are engaged in different language functions (Hickok & Poeppel, 2004; Rolheiser et al., 2011; Weiller et al., 2011; Cloutman, 2012; Friederici & Gierhan, 2013) although they interact in a synergistic way (Rolheiser et al., 2011; Cloutman, 2012; Majerus et al., 2012; Majerus, 2013), so that phonological sequencing and articulation from the dorsal stream operate in concert with the semantic information from the ventral stream to guarantee efficient production and comprehension of language (Turken & Dronkers, 2011; Cloutman, 2012; Friederici & Gierhan, 2013; Rijntjes et al., 2012). Therefore, impaired sentence comprehension and repetition of non-words, word lists and sentences in JAM may be ascribed to the simultaneous damage to the ventral (AF) and dorsal (IFOF) streams.

JAM, and the two previous cases, EDE and JNR (Berndt et al., 1991; Berthier et al., 2011) also had variable cortical involvement which definitely contributed to the observed deficits. Right temporo-parietal involvement (large in EDE and JRN and mild to moderate in JAM) was heterogeneous but consistently involved the right ventral temporal cortex encompassing the temporal stem and its adjoining auditory and visual white matter tracts. Comprehension deficits in acute (Naeser et al., 1982; Kümmerer et al., 2013) and chronic aphasia (Alexander et al., 1989b; Sharp et al., 2004) have been correlated with dysfunction of ventral temporal cortex and interruption of long-distance association (ventral stream—IFOF) and commissural (anterior commissure) cortico-cortical pathways (Sharp et al., 2004; Warren et al., 2009; Turken & Dronkers, 2011; Weiller et al., 2011; Cloutman, 2012; Friederici & Gierhan, 2013). Functional neuroimaging and brain stimulation studies also found that the basal temporal cortex, frontal operculum and the ventral stream are strongly engaged in lexical-semantic and syntactic processing

(Nobre et al., 1994; Sharp et al., 2004; Warren et al., 2009; Rolheiser et al., 2011; Friederici & Gierhan, 2013; Koubeissi et al., 2012; Weiller et al., 2011). In consonance with these data, our patient and the two previously published cases (Berndt et al., 1991; Berthier et al., 2011) had auditory and written comprehension preserved for single words but not for sentences presented in these input modalities. The basal ganglia components of the lesions in our patient involved the anterior commissure (Warren et al., 2009; Catani & Thiebaut de Schotten, 2012) and probably interrupted functional connectivity between homologous regions of the anterior and medial temporal cortex, thus preventing access to meaning in the left temporal cortex during sentence comprehension/production (Umeoka et al., 2009; Warren et al., 2009).

In addition, tissue damage to the right basal temporal cortex is highly likely to disrupt its reciprocal connectivity with the posterior-superior temporal gyrus further hampering phonological processing (Ishitobi et al., 2000; Koubeissi et al., 2012). Therefore, it seems that damage to these structures might have impeded in our patient a compensatory recruitment of the lexical-semantic system in the service of repetition as in usually observed in patients with chronic CA and left hemisphere damage.

LIMITATIONS

One important shortcoming of our study is that formal language evaluations could be performed only in the chronic period. This precluded determining whether some functions were spared (e.g., single word comprehension) because they were unaffected by tissue damage or whether they were abnormal in the early stages and recovered later on reflecting the action of compensatory mechanisms associated with either brain reparation or the recruitment of alternative brain areas. Future studies in aphasic patients like the ones described here should be longitudinal, initiated soon after brain damage, and complemented with multimodal imaging (e.g., fMRI, arterial spin labeling, positron emission tomography) to evaluate dissociation of language functions and also to rule out remote effects in the contralateral hemisphere.

CONCLUDING REMARKS

In conclusion, our findings reveal that patients with crossed CA and right striatal/capsular lesions extending inferiorly to the temporal stem and IFOF and superiorly to the AF and white matter beneath the supramarginal gyrus may show limited access to lexical-semantic information during word list and sentence repetition. Interruption of the long direct segment of the right AF might account for the abnormal performance in word and non-word repetition. Damage to the right ventral stream (IFOF) running between the insular cortex and putamen might be responsible from the impairment of the lexical-semantic and syntactic processing necessary for accurate sentence comprehension and repetition. In addition, the involvement of the right basal temporal cortex (temporal stem, basal language area) may have severed commissural pathways (anterior commissure) disrupting functional connectivity with its homologous counterpart further limiting the access to meaning during sentence comprehension/production (Umeoka et al., 2009; Warren et al., 2009) and also with the posterior-superior temporal gyrus disturbing phonological processing (Ishitobi et al., 2000; Koubeissi et al., 2012). Further analysis of individuals with right hemisphere language dominance is needed to enhance our understanding on the role of white matter tracts in language repetition.

STUDY 3: Cholinergic potentiation and audiovisual repetition-imitation therapy improve speech production and communication deficits by inducing structural plasticity in white matter tracts.

Reference: **De-Torres I.,** Berthier M.L., Paredes-Pacheco J., Poé-Vellvé N., Thurnhofer-Hemsi K., López-Barroso D., Torres-Prioris M.J., Alfaro F., Moreno-Torres I., Dávila G. (2017). Cholinergic potentiation and audiovisual repetition-imitation therapy improve speech production and communication deficits by inducing structural plasticity in white matter tracts. Frontiers in Human Neuroscience (in press).

Abstract - Study 3

We studied longitudinal brain changes in grey matter and white matter tracts in a right-handed male (JAM) with chronic CA and a right subcortical lesion (crossed aphasia) treated with two different interventions. A single-patient, open-label multiple-baseline design incorporating two different treatments and two posttreatment evaluations was used. The patient received an initial dose of DP (5 mg/day) which was maintained during 4 weeks and then titrated up to 10 mg/day and administered alone (without aphasia therapy) during eight weeks (Endpoint 1). Thereafter, the drug was combined with an audiovisual repetition-imitation therapy (Look-Listen-Repeat - LLR) (1 hour/day) during 2 months (Endpoint 2). Language evaluations, DTI and voxel-based morphometry (VBM) were performed at baseline and at both endpoints in JAM and once in 21 healthy controls males. Treatment with DP alone and combined with LLR induced marked improvement in aphasia and communication deficits as well as in selected measures of connected speech production, and verbal repetition. The obtained gains in speech production remained well-above baseline scores even four months after ending combined therapy. Longitudinal DTI showed structural plasticity in the right frontal aslant tract (FAT) and direct segment of the AF

(DSAF) with both interventions. No favourable structural changes were found in other white matter tracts nor in cortical areas linked by these tracts. In conclusion, cholinergic potentiation alone and combined with a model-based aphasia therapy improved language deficits by promoting structural plastic changes in the right white matter tracts.

Introduction - Study 3

The term structural plasticity refers to the brain's ability to actually change its physical structure after repeated practice (Zatorre et al., 2012; Fridriksson and Smith, 2016). Very few studies have explored structural plasticity promoted by intensive therapy or non-invasive brain stimulation in aphasia (Zipse et al., 2011; Allendorfer et al., 2012; Wan et al., 2014). The preliminary evidence suggests thatlocation of structural plastic changes is not random as it probably depends upon the type of therapy (i.e., intensive MIT targets the right AF) (Schlaug et al., 2009; van Hees et al., 2013; Fridriksson & Smith, 2016). However, there are no studies exploring whether structural plasticity can be enhanced combining a cognitive-enhancing drug and intensive therapy in chronic aphasia. Here, we reporta significant improvement ofaphasia severity, everyday communication and speech production (fluency and repetition) in a strongly right-handed male patient (JAM) with chronic CA and a right subcortical haemorrhage (crossed aphasia) while he received the cholinergic agent DP and intensive audiovisual repetition-imitation therapy. Longitudinal brain changes examined with DTI and VBM revealed plastic changes in both the right FAT and the DSAF.

The key role of cortical areas in speech production and communication deficits in aphasia is undisputed (Baldo et al., 2006; Borovsky et al., 2007). Nevertheless, the current notion is that spoken language in normal and pathological conditions depend on large-scale networks that orchestrate the activity of specific brain regions via long-range white matter connections (see Simonyan et al., 2016; Halai et al., 2017). The impetus to examine structural plasticity in white matter tracts in JAM comes from findings of recent neuroimaging studies of white matter pathways underpinning speech production. A major contribution of two tracts (FAT and anterior segment of the AF - ASAF) to speech fluency together with other components of the speech production network has been demonstrated (Fridriksson et al., 2013; Basilakos et al., 2014). The FAT is a newly identified pathway in post-mortem dissections (Vergani et al., 2014), direct electrostimulation (Vassal et al., 2014), and DTI (Klein et al., 2007; Ford et al., 2010; Catani & Thiebaut de Schotten, 2012, Catani et al., 2013, Kronfeld-Duenias et al., 2014; Broce et al., 2015). The FAT directly connects the pre-supplementary motor area (pre-SMA), SMA and anterior cingulate areas with the pars opercularis of the inferior frontal gyrus (Catani et al., 2013; Vergani et al., 2014). Regarding the functions of cortical areas linked by the FAT, the pre-SMA is related to linguistic processing and cognitive control (Catani et al., 2013; Hertrich et al., 2016), whereas the SMA proper participates in speech motor control (initiation, coordination and speech monitoring) (Laplane et al., 1977; Crosson et al., 2001; Alario et al., 2006; Hertrich et al., 2016). The pre-SMA and SMA participate on planning and motor initiation and interact with the executive motor cortex via the basal ganglia (motor loop) and thalamus (Bohland et al., 2006, 2009). Lesion mapping studies show that damage to medial frontal cortex (pre-SMA and SMA) interrupting (or not) the FAT has been associated with speech arrest (Martino et al., 2012), reduced speech fluency (Catani et al., 2013;

Balisakos et al., 2014; Kronfeld-Duenias et al. 2014), and impaired morphological derivation of verbs (Sierpowska et al., 2015). Another white matter tract implicated in speech fluency is the ASAF, which links the inferior parietal lobe with an inferior frontal region important for planning speech production (Marchina et al., 2011; Fridriksson et al., 2013; Basilakos et al., 2014; Pani et al., 2016). However, the AF has traditionally been related to verbal repetition (Geschwind, 1965), although it may be divisible into three segments which support different functions. Verbal repetition has been linked with the activity of the long segment and the posterior segment of the AF (Saur et al., 2008; Catani & Thiebaut de Schotten, 2012), whereas its anterior segment has been related to speech production and conversation (Catani et al., 2013).Despite that the ASAF overlap with the FAT in the deep region beneath the Brodmann's area 6, it has been suggested that damage to the ASAF and the FAT plays an independent yet synergistic deleterious effect on speech fluency in brain damaged subjects (Basilakos et al., 2014).The role of the uncinate fasciculus in speech fluency is more controversial (see Fridriksson et al., 2016; Basilakos et al., 2014; Hope et al., 2016).

An important question that now arises is whether the structure of these white matter tracts can be successfully modified with biological approaches (drugs, non-invasive brain stimulation) and model-based aphasia therapies. Brain remodeling promoted by intensive aphasia therapiesis increasingly studied with neuroimaging methods. Intervention studies used repetition training in the presence of a picture (Heath et al., 2012) or embedded in MIT (Sparks et al., 1974; Schlaug et al., 2009; Zipse et al., 2012) and CIAT (Pulvermüller et al., 2001; Breier et al., 2011) with the aim of activating the remnants of left white matter pathways (AF) and/or to stimulate the compensatory activity of their homologues counterparts in the right hemisphere when the left ones are enduringly damaged. Improvements were found in picture naming (Heath et al., 2013; van Hees et al., 2013) and speech production (Schlaug et al., 2009; Breier et al., 2011; Zipse et al., 2012) and attributed to therapy-promoted strengthening of auditory-motor assemblies or semantic-phonological connections in the right hemisphere (Zipse et al., 2012; Heath et al., 2012). The effectiveness of rehabilitation to improve aphasia outcomes is often limited, particularly in patients with extensive damage to the language areas. Therefore, biological therapies (drugs and non-invasive brain stimulation) are increasingly used to augment and accelerate the benefits provided by aphasia therapy. In previous studies, gains in speech production have been augmented combining model-based aphasia therapies and excitatory repetitive transcranial magnetic stimulation (rTMS) (Al-Janabi et al., 2014; see also Restle et al., 2012), excitatory (anodal) transcranial direct current stimulation (anodal-tDCS) (Vines et al., 2011) and cognitive-enhancing drugs (Berthier et al., 2014).

Drug therapy plays animportant role in the treatment of language deficits in chronic stroke patients with aphasia (Berthier & Pulvermüller, 2011; Berthier et al., 2011; Llano & Small, 2016). Berthier et al. (2014) used massed sentence repetition therapy (40 hours) to treat three patients with chronic post-stroke CA and large left hemisphere lesions who were receiving a cholinergic agent (DP). This combined intervention augmented and speeded up benefits in speech production deficits previously obtained in these patients with DP and distributed speech language therapy (40 hours) (Berthier et al., 2014). In recent years, however, speech pathologists recognize that auditory repetition practice alone is not enough to promote manifest benefits in everyday language activities and functional communication (Lee et al., 2010; Fridriksson et al., 2012; 2013). Therefore, repetition-imitation of audiovisual stimuli have been used to treat aphasia (Lee et al., 2010; Fridriksson et al., 2012; 2013; Heath et al., 2012, 2013). The rationale behind two recently developed therapies namely Intensive Mouth Imitation and Talking for Aphasia Therapeutic Effects (IMITATE) (Duncan & Small, 2016) and Speech Entrainment (Fridriksson et al., 2012, 2013) is using action observation and imitation of visual and auditory stimuli to enhance the activity of bilateral parietal-frontal pathways (audiovisual mirror neurons) (Mashal et al., 2012; Duncan & Small, 2016) and ventral language streams (Fridriksson et al., 2012, 2013). The idea behind these therapies was taken as a basis to develop our method called “Look, Listen and Repeat” (LLR) (www.repiteconmigo.es) to improve speech production deficits and communication in JAM.

Methods - Study 3

CASE DESCRIPTION

PATIENT JAM

JAM was a 46-year-old right-handed, monolingual male with no history of neurological disease, no family history of left-handedness, and normal developmental milestones (see further details in De-Torres et al., 2013). His personal history was remarkable for hypertension and type II diabetes. He suffered a right striatal-capsular haemorrhage associated with global aphasia, left hemianopia, and dense left hemiparesis with impaired sensation. According to the hospital report, as inpatient JAM suffered a single epileptic attack and at the time of discharge (15-days post-onset) he had fluent jargon aphasia and impaired comprehension. Reading and writing were also severely impaired. Four-months post-onset (one year before entering the drug trial), he was depressed with a tendency to social withdrawal (Hamilton Depression Rating Scale score: 14 - Hamilton, 1960). A treatment with escitalopram (20 mg/day) was associated with an improvement of depressive symptoms in the next few months. The first formal evaluation of JAM in the Unit of Cognitive Neurology and Aphasia wasperformed 16 months after the haemorrhage. By that time, he showed a dense left hemiparesis (Fugl-Meyer Scale: left upper limb: 5/66; left lower limb: 7/34) (Fugl-Meyer, 1975), mild mobility problems (Rivermead Mobility Index: 13/15) (Collen et al., 1991) and moderatedependency for activities of daily living (bathing, dressing, feeding, and grooming) (Barthel dependency index: 50/100-Mahoney and Barthel, 1965). In spite of having a large right subcortical lesion, he did not show anosognosia or neglect. On the Stroke Aphasia Quality of Life 39 (SAQoL-

39) (Hilari et al., 2003) he obtained an average score of 2.28 (physical 2.23, communication 3; psychosocial 1.8, and vitality 2).

STUDY DESIGN

A single-patient, open-label multiple-baseline design in corporating two treatment and two posttreatment evaluations was used (Figure 5). The design used was an A-B-BC-D1-D2. Following the establishment of a stable baseline (A), the patient received DP 5 (mg/day) during 4 weeks and then the dose was increased (10 mg/day) during 12 weeks without speech-language therapy in either phase (B). Thereafter, the patient continued with DP (10 mg /day) combined with LLR therapy (BC). After ending combined therapy, there were two washout periods of both DP and LLR (D1-D2). These effect sizes relate to the phase comparisons of A-B (baseline to the first intervention phase - week 0 vs week 16), B-BC (the first treatment phase to second treatment phase - week 16 vs week 28), BC-D1 (the combined treatment to the first posttreatment evaluation - week 28 vs week 36), BC to D2 (the combined treatment to the second posttreatment evaluation - week 28 vs week 44). Language evaluations were performed at baselines (week 0), endpoints B (week 16) and BC (week 28) and at follow-ups (week 36 and week 44). Other pharmacological treatments (escitalopram, losartan and sitagliptin/ metformin, omeprazole, baclofen, and levetiracetam) were kept unchanged during the trial. The study was performed according to the Declaration of Helsinki and the protocol was approved by the Local Community Ethics Committee for Clinical Trials and the Spanish Medical Agency. This single case study was conducted as part of an independent research project funded by Pfizer/Eisai, Spain and it was designed, conducted and controlled by the principal investigator (MLB). The study was registered with EudraCT number 2008-008481-12.

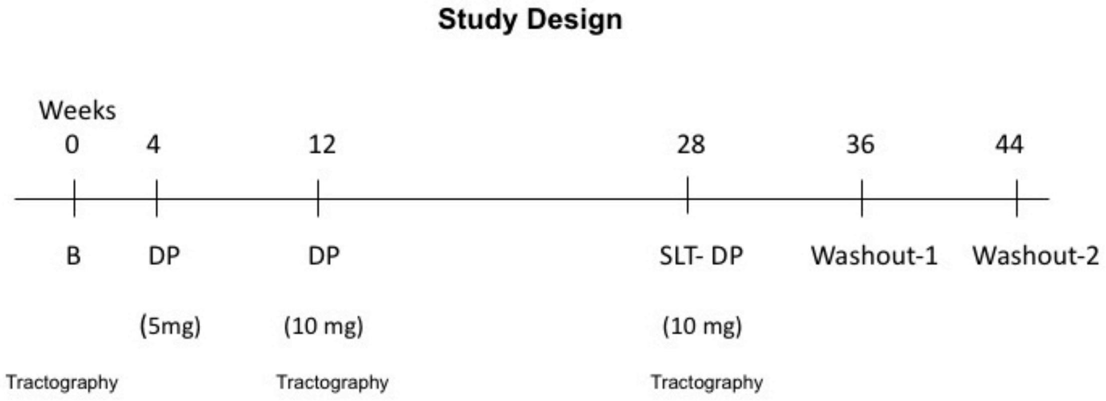

Figure 5. Study 3 design. A single-patient, open-label multiple-baseline design in corporating two treatment and two posttreatment evaluations was used. Following the establishment of a stable baseline, the patient received DP 5 (mg/day) during 4 weeks and then the dose was increased (10 mg/day) during 12 weeks without speech-language therapy in either phase. Thereafter, the patient continued with DP (10 mg /day) combined with LLR therapy. After ending combined therapy, there were two washout periods of both DP and LLR.

DRUG TREATMENT

The drug used was DP (orally disintegrating tablets of 5 mg and 10 mg). The dose of DP of 10 mg/day represents the dose used in well-designed studies of post-stroke aphasia (Berthier et al., 2006; Woodhead et al., 2017). Compliance was determined at every visit by tablet counts. DP tablets were provided by Pfizer/Eisai, Spain. The detection of potential adverse events was monitored during the trial.

APHASIA THERAPY

STIMULI SELECTION PROCEDURE

All sentences included in the Look-Listen-Repeat (LLR) therapy (www.repiteconmigo.es) were composed of words of high frequency, high imageability, and predictability with an increasing length and grammatical difficulty. Individual words were selected from LEXESP (Léxico informatizado del español -Sebastián-Gallés et al., 2000). Sentences included words belonging to highly familiar semantic categories for both nouns (food, animals, places, transport, nature, household objects, everyday objects, nature, body parts, clothing, professions, ages, gender, family) and adjectives (colours, sizes, appearances, character). Three levels of difficulty were developed and there were several lists. The first level of difficulty contained three lists of 30 sentences construed with the following sentence structure: subject-verb (i.e,, "The child runs"); verb-direct object (i.e., "Give me the bread"), and copulative sentence (i.e., "The child is nice”). The second level consists of four lists of 50 sentences each with sentences like: subject-verb-object (i.e., "The boy stood on a chair"), noun-adjective-verb (i.e, "The child runs nice"); and temporal/spatial complements: (i.e.,"The child comes tomorrow"). It was planned a more complex third level that was not used with JAM because the second level was challenging enough to him and permitted a good working level. For the third level, a list of 25 more complex sentences was construed including frames like: (i.e., "The boy who lives here is friendly") and sentences with subordinate clauses with thought verbs (i.e., "Angel believes that her mother will not come") and temporal subordinate clauses (i.e., "I’ll get it when I go home").

AUDIOVISUAL RECORDINGS

Five adult healthy subjects of both sexes and varying ages (three females and two males, age range: 20-50 years) collaborated in recording the audiovisual stimuli. All five speakers were native speakers from Spanish. Only the speaker's upper body and head were recorded, and the hands were specifically excluded from the recordings. Each speaker was centered in the frame for all stimuli. The speakers were instructed to say the words and phrases as they would occur in everyday language. Speakers were told to start and end each clip with the mouth closed, looking directly at the camera. It was very important that the stimuli be as ecological as possible. For each stimulus, after the speaker appears, there is a brief delay before the initiation of speech, followed by production of the word or phrase and finally a brief delay after the speaker has completed voicing of the word.

TREATMENT PROCEDURE

In the baseline assessments it was noted that JAM presented no difficulty in repeating single words and some nonwords, showing variable difficulty with the repetition of two-word and three-word lists and sentences (see De-Torres et al., 2013). Therefore, the aphasia therapy program was tailored to treat the greater JAM's difficulty: sentence repetition (see Salis et al., 2015; Eoma & Sunga, 2016) with the aim of improving speech fluency (Kohn et al., 1990). The therapy was called Look-Listen-Repeat (LLR). Repetition task was developed by videotaped lists of sentences. JAM saw the face of a person in a videotape saying a sentence to the camera, and then he had a time of five seconds to repeat the prayer. The patient get both phonological and audio-visual input of oral and facial mimicry.

The lists presented 50 sentences each, except the first introductory three sentences (Level I) that were shorter (30 sentences). The average number of words per sentence in Level I was 4.46 and 6.10 in Level II. JAM was asked to repeat each list at least twice in the morning and twice in the afternoon. JAM was evaluated weekly in the execution of the therapy. The list were changed weekly when the objective was achieved (90% of stimuli were well-repeated). JAM was supposed to train sentence repetition unless 20 minutes twice a day for a period of 20 weeks. It was not planned for JAM training with lists of sentences with delayed repetition, because repeating withoutdelay posed a sufficient degree of difficulty for him.

BASELINE TESTING

Language and communication were assessed in two occasions before initiating treatment. The first linguistic evaluation was performed in September 2011 (at the end of general cognitive testing) (see De-Torres et al., 2013), whereas the second linguistic evaluation was performed in April 2012. JAM patient did not receive any type of speech and language therapy between the first and second baseline evaluations.

OUTCOME MEASURES

APHASIA SEVERITY

The severity of aphasia was rated at baseline and at two different time points using the WAB - Aphasia Quotient (WAB-AQ). Two further evaluations were also carried out after ending both treatments. The WAB-AQ is a measure of aphasia global severity, which is sensible enough to detect longitudinal changes after treatment of post-stroke aphasia with different cholinergic agents (Berthier et al., 2006; Chen et al., 2010; Hong et al., 2012; Yoon et al., 2015). Increases in the WAB-AQ scores ≥ 5 at the two endpoints (B and BC) and two washouts (D1 and D2) in comparison to baseline (A) were considered positive responses to the interventions (Cherney et al., 2010; Berthier et al., 2011).

COMMUNICATION IN ACTIVITIES OF DAILY LIVING

Communication in activities of daily living was assessed with the Communicative Activity Log (CAL) (Pulvermüller & Berthier, 2008). The CAL was completed by the spouse of JAM in the presence of one member of the research team in order to clarify potential misunderstanding of questions’ content or scoring. The CAL is composed of 36 questions divided in two parts that address quality of communication (e.g., ‘‘How well would the patient verbally express criticisms or make complaints?’’) and amount of communication (e.g., ‘‘How frequently would the patient verbally express criticisms or make complaints?’’). The CAL’s quality of communication score is obtained by summing up scores for items 1-18. The amount of communication score is obtained by summing up scores over items 19-36. Scores range from 0 to 180 and high scores indicate better everyday communication. In previous intervention studies, the CAL has been found to be sensible enough to detect beneficial longitudinal changes (Berthier et al., 2009; Difrancesco et al., 2012; Kurland et al., 2012; Mohr et al., 2016).

SPEECH PRODUCTION

To examine connected speech production, speech samples in one baseline, two treatment and two post-treatment phases were obtained from the Picnic Scene picture description of the WAB during a time limit of 5 minutes with the same methodology used in other patients with CA and treated with a similar therapy (Berthier et al., 2014). All descriptions were audiotaped and transcribed by one of us (MLB). There are no fully accepted rules for rating verbal production during picture description in aphasia. Although measures to rating spontaneous speech (fluency and information content) of the WAB have been used in previous studies (Basilakos et al., 2014) there is general agreement that these measures are to a certain extent unreliable. In the present case, speech samples were analyzed using a more reliable methodology (Nicholas & Brookshire, 1993; Marchina et al., 2011; Zipse et al., 2012; Wang et al., 2013, Berthier et al., 2014). The following metrics were examined: number of words, number of words/minute (speech rate), correct information units (CIU) and percentage of CIUs. A CIU is defined as as non-redundant content words that convey correct information about the stimulus (Nicholas & Brookshire, 1993). To be classified as CIUs, words should be not only intelligible in context, but also accurate, relevant and informative with respect to the stimulus (Nicholas & Brookshire, 1993). Meaningless utterances, perseverations, paraphasias and other inappropriate information (exclamations) were counted as words, but not classified as CIUs. The percentage of correct information units (%CIU) was established using the following formula: number of CIUs/number of words x 100.

REPETITION

WORDS AND NONWORDS

Repetition of words and nonwords was evaluated with test 9 (Repetition: Imageability x Frequency) of the PALPA (Kay et al., 1992; Valle & Cuetos, 1995). This test contains 80 words and 80 non-words presented in a mixed fashion. Words were grouped in four lists (20 items in each list) with variations in frequency and imageability. The lists contained high-frequency / high-imageability, high-frequency / low-imageability, low-frequency / high-imageability, and low-frequency / low-imageability words. These lists were matched for syllable length; items contained between one and four syllables. The non words were matched to the words for phonological complexity.

SENTENCES

Repetition of sentences was tested with test 12 (Repetition: Sentences) from the PALPA battery (Kay et al., 1992; Valle & Cuetos, 1995). This task evaluates the ability to repeat auditorily-presented sentences (n = 36) of different length (from 5 to 9 words). It is composed of reversible sentences (n = 20) and non-reversible (n = 16) sentences.

IDIOMATIC PHRASES AND NOVEL PHRASES

Since the production of idiomatic expressions (also called formulaic language) primarily depends on the activity in right-hemisphere neural networks (cf. Berthier et al., 2014; Stahl & Van Lancker Sidtis, 2015), a set of familiar idiomatic Spanish sentences (clichés) (n = 40) taken from the 150 Famous Clichés of Spanish Language (Junceda, 1981) was used in repetition. Moreover, previous studies on

CA revealed a dissociation in the ability to repeat clichés as compared to novel sentences (McCarthy & Warrington, 1984). Therefore, a control a set of novel sentences (n = 40) matched with the idiomatic phrases was also tested for auditory repetition (Berthier et al., 2014). For example, for the idiomatic cliché: “Me lo dijo un pajarito” (“A little bird told me”) the novel control phrase: “Me lo dijo mi compadre” (“My friend told me”) was created.

NEUROIMAGING

IMAGE ACQUISITION

MRI data were acquired on a 3-T MRI scanner (Philips GyroscanIntera, Best, The Netherlands) with an eight-channel Philips SENSE head coil. Head movements were minimized using head pads and a forehead strap.

High-resolution T1 structural images of the whole brain were acquired for the patient JAM at three time points: Baseline, (week 0), DP (week 12) and DP+therapy (week 28). The T1-weighted scans were also obtained for 22 healthy control subjects, matched with JAM by sex (all controls were male) and age (mean age: 33.05 ± 10.03 years; range: 22-59 years). The acquisition sequence was three-dimensional magnetization prepared rapid acquisition gradient echo (3D MPRAGE), with the following parameters: acquisition matrix, 268/265; field of view, 224 mm; repetition time (TR), 9.2 ms; echo time (TE), 4.2 ms; flip angle, 8º ; turbo field echo (TFE) factor, 200; reconstruction voxel size, 0.68 mm × 0.68 mm × 0.8 mm. Two hundred and ten contiguous slices were acquired, with 0 mm slice gap. The total acquisition time of the sequence was about 3 min.

DTI data acquisition was performed for the patient at the three aforementioned time points, using multi-slice single-shot spin-echo echo planar imaging (EPI) with specific parameters as follows: FOV = 224 mm x 224 mm x 120 mm, 2 mm thick slices with no gap, TE = 117 ms, TR was about 12500 ms, reconstruction matrix = 128 voxels x 128 voxels, 32 diffusion directions with b = 3000 s/mm2, EPI echo train length: 59.

DIFFUSION WEIGHTED IMAGING (DWI)

DWI data were analysed using FSL, MRtrix3 v0.3.15 (http://www.mrtrix.org/), NiBabel v2.1 (http://nipy.org/nibabel/) and Trackvis software packages. The data was denoised using MRtrix3. Motion and eddy current correction were perfomed using FSL. The estimated movements of the participants never exceeded 2 mm or 1.5º in any direction. A brain mask was generated using FSL. After that, the reconstruction and tracking of FAT and AF were carried out with MRtrix3 by combining the Constrained Spherical Deconvolution (CSD) reconstruction method (Tournier et al., 2007) with probabilistic streamlines tractography (Tournier et al., 2010; Tournier el al., 2012). This significantly reduces the crossing fiber problem in diffusion images (Tournier et al., 2008). The main parameters used were: mask = whole brain mask, tracking algorithm = iFOD2, number of generated streamlines = 1.000.000. Also, in the case of FAT, the seed image was a 25 mm radius sphere in the pre-supplementary/supplementary motor area (pre-SMA and SMA), and in the case of AF was a 20mm radius sphere in the inferior parietal lobule.

NiBabel was used to transform the obtained tractograms into a readable format for Trackvis, which allowed a flexible 3D visualization of the tracts. In particular, the output of tractography generation and the b0 image were used to generate the tract-files using tck2trk tool in NiBabel. Trackvis was used to visualize the tract-files. The FAT was examined using spheres in the posterior inferior frontal gyrus, pars opercularis (IFGOp) and pre-SMA/SMA to isolate the right and left aslant tracts (Catani & Thiebaut de Schotten, 2012). The segments of the AF were examined using three ROIs in the Broca's, Wernicke's and Geschwind's areas (Catani & Thiebaut de Schotten, 2012). Spurious fibers were removed from the tracks by using an additional avoidance ROI (logical NOT operation). The FAT and the AF were dissected in both cerebral hemispheres.

WHITE MATTER VOXEL-BASED MORPHOMETRY

VBM analysis was performed using statistical parametric mapping (SPM12), (http://www.fil.ion.ucl.ac.uk/spm/), running on MATLAB R2013b (Mathworks Inc., Natick, MA, USA). All T1 structural images were AC-PC oriented. A lesion mask, drawn over the T1-weighted images of JAM for each time point, was applied to T1 images of the patient. Then, the T1-weighted images were segmented into grey matter, white matter and cerebrospinal fluid tissue classes. They were normalized into the MNI space with modulation option and smoothed with an 8 mm FWHM kernel. The lesion masks were also normalized. A mask of the FAT and another of the AF were generated using Trackvis v0.6.0.1 (http://www.trackvis.org/). In the case of FAT, the mask was based on the diffusion images (see next section) obtained at the third time point. In the case of the AF, the left direct segment, the left posterior segment, the right posterior segment and the right anterior segment were selected from the first time point, and the right direct segment and the left anterior segment were obtained from the second time point. In all cases, the chosen tracts were those with larger volume and better definition. These masks were coregistered to each of the three T1-weighted images of the patient. To do so, the b0 image used to derive the mask was coregistered to each T1 scan using the FLIRT and FNIRT commands of FSL v5.0.9 (http://www.fmrib.ox.ac.uk/fsl/). The obtained transformations were then applied to the masks. The coregistered masks were normalized into the MNI space by applying the forward deformation field of each T1-weighted image. The final masks were generated subtracting the lesion from the normalized FAT masks and from the normalized AF masks. The white matter segment of each time point was then compared to the white matter segments of the controls in a VBM analysis. Only the areas of FAT and AF were studied, applying small volume correction (SVC) with the normalized masks for each time point. The applied contrast was Control > JAM. The contrast JAM > Control did not yield any significant results.

Results - Study 3

LANGUAGE AND COMMUNICATION FINDINGS

Two baseline assessments revealed stable deficits in language (WAB-AQ, baseline 1: 78.8; baseline 2: 79.6) and everyday communication (CAL total, baseline 1: 113; baseline 2: 113) so that it seemsthat the benefits obtained in JAM were the direct effect of both treatments. A progressive improvement in both the WAB-AQ and CAL scores was observed at the twoendpoints. Moreover, these benefits remained well-above baseline scores in the two washout evaluations performed several weeks after ending both interventions (Table 7, Figure 6). On the WAB-AQ scores, a measure of aphasia severity, treatment with DP alone (week 12) was associated with a gain of 8.7 points relative to baseline assessment (p = 0.008) , an increment that allows classifying JAM as a responder to the drug (Cherney et al., 2010; Berthier et al., 2011). A further increment on the WAB-AQ (10.4 relative to baseline) when this dose of DP was combined with intensive and prolonged LLR therapy (week 28, p = 0.002). However, although scores on the WAB-AQ were higher with DP-LLR than with DP alone, this difference did not reach statistical significance (p =0.500). These gains remained stable in the first posttreatment evaluation (week 36, gain in AQ: 8.1, p = 0.008 compared to baseline) but not in the second posttreament testing (week 44, gain in AQ: 4.9, p = 0.125compared to baseline). Several verbal subtests of the WAB contributed to increase the AQ scores in the two endpoints, most notably (comprehension and repetition).

The CAL’s total and the two subscales (quality and amount of communication) showed significant increases in comparison with baseline under treatment with

DP alone (10 mg/day, week 16) (all p= 0.0001) and when DP was combined with LLR therapy (all p= 0.0001). Moreover, scores on CAL's total and the quality of communication subscaleimproved more with combined DP-LLR therapy (week 28) than with DP alone (week 16) (both p = 0.016), but no changes were found in the amount of communication between these two endpoints (p = 0.100). The significant gains on CAL's total score and on its subscales were maintained during the two washout evaluations (weeks 36 and 44) (both p = 0.0001).

CONNECTED SPEECH PRODUCTION FINDINGS

All four parameters improved throughout the trial (Table 7), yet the most noticeable gains were found under DP alone (week 0 to week 16). A mild decrease in all these parameters was found with combined DP-LLR (week 28) in comparison with DP alone (week 16). Improvements with both interventions remained well above baseline scores in the two washout evaluations performed several weeks after ending the trial.

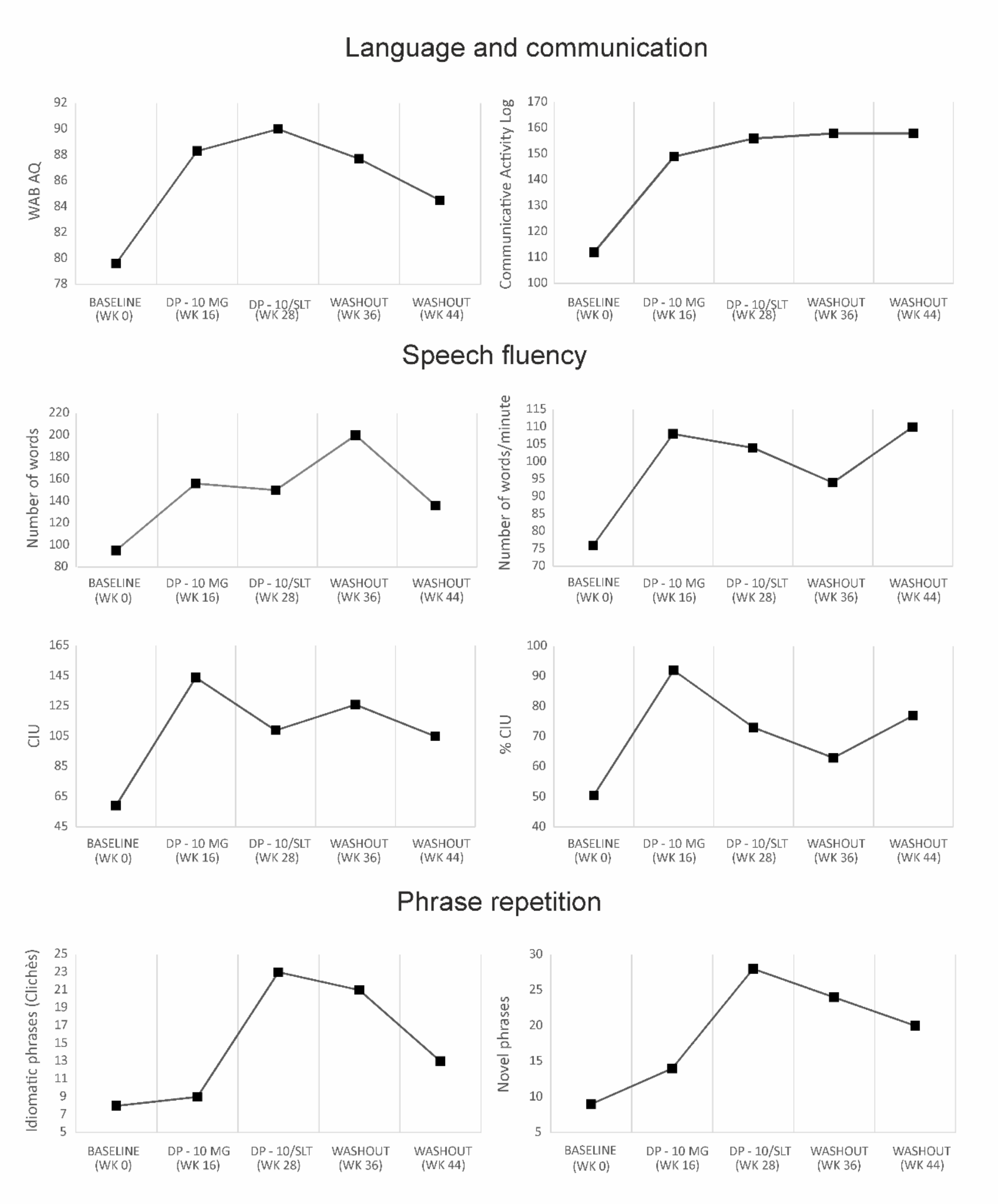

Figure 6. The graphs depict performance on language (WAB-AQ) and everyday communication (Communicative Activity Log), four measures of speech fluency, and repetition of idiomatic clichés and novel phrases at baseline, two endpoints, and two washout periods. The most impressive beneficial changes in language and communication and in measures of speech fluency (number of words, number of words per minute, correct information units [CIU] and % of CIU) were observed with DP alone (week 0 *vs.* week 16). As expected, the action of DPwas enhanced on repetition of clichés and novel phrases during audiovisual repetition-imitation training (week 16 vs. week 28). WAB-AQ indicates Western Aphasia Battery. See further details in text.

Table 7 | Performance of patient JAM on language, communication, speech fluency and repetition tasks at baseline, two endpoints and two washout evaluations.

7A. Language and Communication Measures	Baseline (Wk 0)	DP-10 mg (Wk 16)	DP-10/SLT (Wk 28)	Washout-1 (Wk 36)	Washout-2 (Wk 44)
Western Aphasia Battery (WAB)					
Aphasia Quotient (max = 100)	79.6	88.3	90.0	87.7	84.5
Fluency (max = 10)	8	9	9	9	9
Comprehension (max = 10)	8.5	9.25	9.4	8.75	8.95
Repetition (max = 10)	6	7.4	7.8	7.7	8.4
Naming (max = 10)	8.9	9.5	9.8	9.4	6.4
Communicative Activity Log, total	112	149	156	158	158
Frequency	54	76	76	77	77
Quality	59	73	80	81	81

7B. Speech fluency in connected speech Measures	Baseline (Wk 0)	DP-10 mg (Wk 16)	DP-10/SLT (Wk 28)	Washout-1 (Wk 36)	Washout-2 (Wk 44)
WAB - Picture description					
Number of elements described	14	18	20	18	18
Number of words	95	156	150	200	136
Number of words/minute	76	108	104	94	110
Time (seconds)	75	86	104	128	74
Correct information units (CIU)	59	144	109	126	105
% CIU	51	92	73	63	77
CIU/minute	38	100	76	59	85

7C. Repetition of words and sentences Measures	Baseline (Wk 0)	DP-10 mg (Wk 16)	DP-10/SLT (Wk 28)	Washout-1 (Wk 36)	Washout-2 (Wk 44)
Word repetition (n = 80) (PALPA 9)	69	75	75	78	79
Sentences (PALPA 12)	8	11	12	10	11
Idiomatic sentences (clichès) (max = 40)	8	9	23	21	13
Novel sentences (max = 40)	9	14	28	24	20

REPETITION

Repetition of words (PALPA 9) showed significant improvements in the two endpoints (weeks 16 and 28) in comparison with baseline assessment (both p = 0.031), but there were no differences between them (p = 0.100) (Table 7). Improvements were maintained in both posttreatment evaluations (weeks 36 and 44) (both p< 0.005). No significant benefits were found in Sentence Repetition (PALPA 12) with either intervention. Treatment with DP alone (week 16) failed to improve repetition of idiomatic (clichès) phrases (p = 0.100), but there was a strong trend for improvement in repetition of novel phrases (p = 0.063). The combined intervention with DP-LLR therapy (week 28) significantly improved JAM's performance on repeating idiomatic clichés and novel phrases (both p = 0.0001) and this intervention was significantly better than the treatment with DP alone (week 28 vs week 16; both tasks p = 0.0001). In addition, these gains remained stable in both posttreatment evaluations for novel sentence repetition (week 36: p = 0.0001; week 44: p = 0.001) and only at the first posttreatment evaluation for idiomatic clichés repetition (week 36, p = 0.0001) although there was a trend for improvement in this task at the second posttreatment evaluation (week 44, p = 0.063).

NEUROIMAGING FINDINGS

LESION LOCATION AND VOLUME

The structural MRI showed a large deep lesion involving the putamen, part of the external pallidum, and anterior limb, genu, and posterior limbs of the internal capsulae (Figure 7). The lesion extended superiorly to the periventricular white matter (corona radiata). There also was tissue damage in the white matter surrounding the hippocampus and the middle temporal gyrus with posterior extension to the auditory and optic radiations in the temporal. The right posterior ventral and dorsal insular cortices and the periventricular white matter deep to the supramarginal gyrus were also damaged. It was noteworthy that although the initial MRI scan was obtained in the chronic period (16-months post-stroke onset) the volume of the lesion expanded in the third MRI (week 28 after study entry) due to enlargement of its more superficial components at the level of the insular cortex (Figure 8). The observed lesion expansion probably resulted from retraction of cortical temporal tissue due to focal post-stroke atrophy.

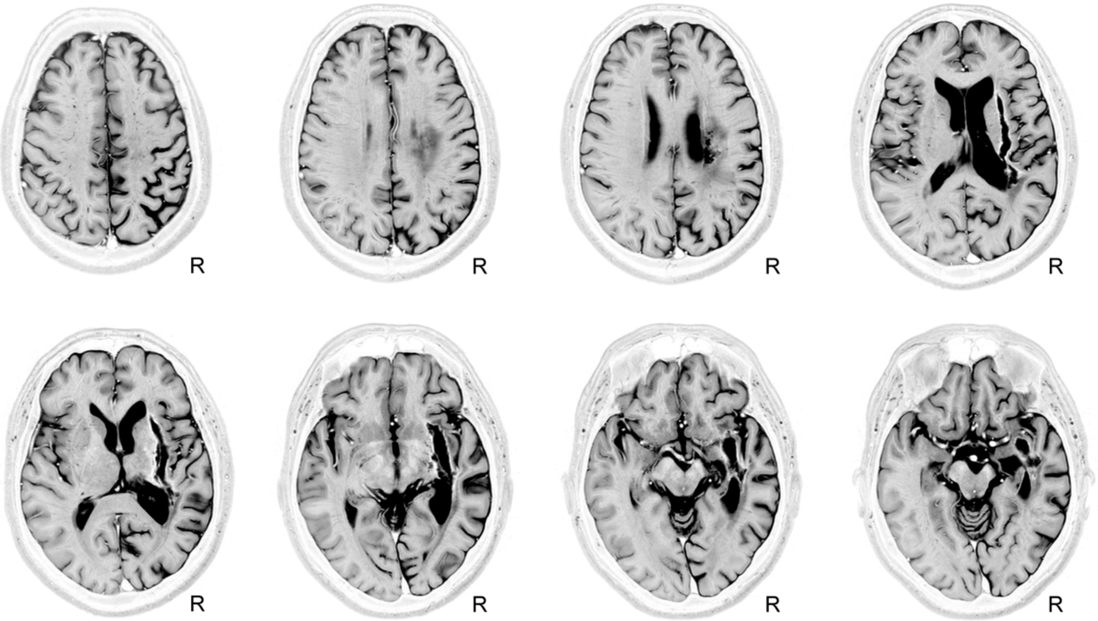

Figure 7. Depiction of an old right subcortical haemorrhage on a T1-weighted MRI sequence.Axial (top row), sagittal (medial row) and coronal (bottom row) views in native space. The MRI showsanextensive lesion with a semilunar configuration involvingthe right striatum-capsular region extending into the surrounding white matter. See text for further details. The neurological convention is used. R: right.

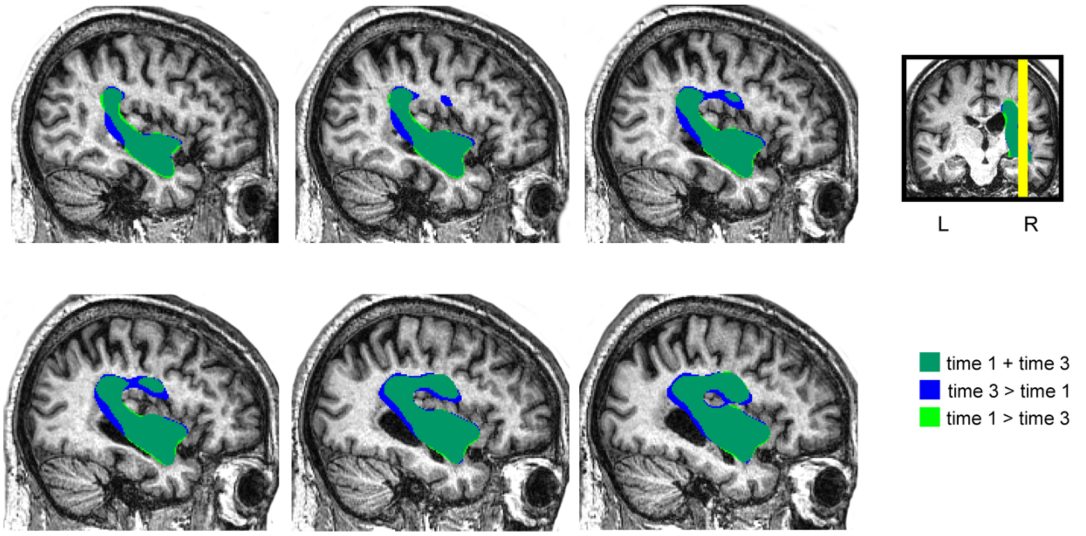

Figure 8. Depiction of the patient's lesion mask in the timepoint 1 (BL) and in the timepoint 3 (DP + T) over the patient's normalized sagittal T_1-weighted image. The lesion mask drawn of the initial MRI (16 months post-stroke onset) was larger in the third MRI (28 weeks after study entry) due to expansion of itssubinsular component. The observed lesion expansion probably resulted from retraction of cortical tissues due to focal temporal post-stroke atrophy (not shown).

DIFFUSION TENSOR IMAGING: TRACTOGRAPHY

In vivo dissection using two ROIs approach of the FAT (Catani et al. 2012) revealed that this pathway was well-preserved in the right hemisphere in spite of the lesion (Figure 9). Volume was measured along the reconstructed FAT streamlines independently for right and left hemispheres. Volume measures along the three time points suggested an initial asymmetrical pattern of distribution which became more symmetrical across the next evaluations (Baseline: left FAT: 22.08ml; right FAT: 11.97ml; DP: left FAT: 19.29ml; right FAT: 14.51ml; DP-LLR therapy: left FAT: 22.45ml; right FAT: 18.77ml). To confirm this finding, a lateralization index (LI) was calculated as follow: (Right vol. - Left vol.) / (Right vol. + Left vol.). The LI has previously been used to assess microstructural differences in white matter pathways between the cerebral hemispheres (Catani et al., 2007; Lopez-Barroso et al., 2013). The LI ranges between −1 and +1, where negative values represent left lateralization, values around zero represent symmetrical distribution, and positive values a right lateralization. The patient´s FAT showed a LI = -0.29 in the baseline phase; LI= -0.14 in DP phase; and LI = -0.08 in DP-LLR therapy phase. Thus, the FAT showed a more symmetrical pattern of distribution after the combined DP-LLR therapy treatment, suggesting that the structural reorganization of this pathway was related to the intervention and the associated improvements in fluency.

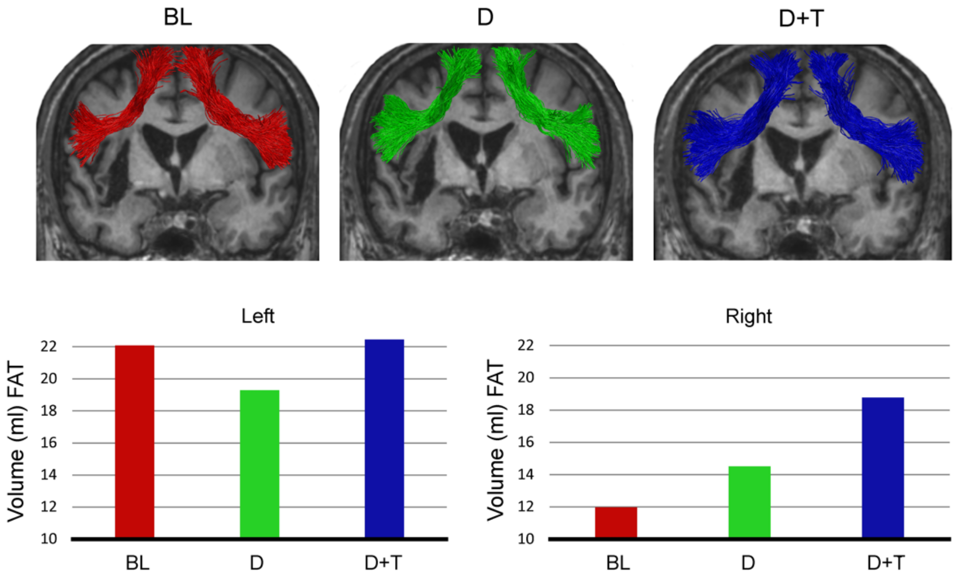

Figure 9. Tractography reconstruction of the left and right frontal aslant tracts (FAT) on the coronal plane in the three different timepoints. White matter microstructural changes are observed in the FAT in the baseline (BL), after drug treatment with Donepezil (D) alone and after combined Donepezil andtherapy (D+T). At the top, the FAT is showed bilaterally overimposed on the T_1-weighted patient´s image in native space. At the bottom, the FAT volume is plotted graphs for each hemisphere. Note that the volume pattern of the left FAT is more stable than the volume of the right FAT which increases progressively across the study phases. Neurological convention is used. R.

Virtual dissection of the AF was performed separately for the anterior, the posterior and the direct segments using a 2 ROIs approach in both hemispheres. The three segments of the AF were reconstructed bilaterally. Volume measures for the three segments along the three time points showed different patterns of symmetry (Baseline: left anterior segment: 16.45ml; left posterior segment: 11.5ml; left direct segment: 42.1ml; right anterior segment: 17.25ml; right posterior segment: 6.93ml; right direct segment: 13.37ml; DP: left anterior segment: 18.8ml; left posterior segment: 9.21ml; left direct segment: 39.86ml; right anterior segment: 13.53ml; right posterior segment: 2.94ml; right direct segment: 16.59ml; DP-LLR therapy: left anterior segment: 16.6ml; left posterior segment: 8.89ml; left direct segment: 31.2ml; right anterior segment: 14.08ml; right posterior segment: 4.21ml; right direct segment: 17.48ml). The LI revealed that the direct segment was more left lateralized at the baseline evaluation (LI=-0.51) and became more symmetrical (DP, LI= -0.41; DP-LLR therapy LI = -0.28).

WHITE MATTER VOXEL-BASED MORPHOMETRY

The white matter volume of each timepoint was compared to the white matter of the controls in a VBM analysis for regions of interests comprising the regions of the FAT and the AF. For the FAT, the applied contrast Control > JAM revealed different significant clusters in the white matter which correspond with the FAT in the right hemisphere, showing that the volume in these regions was lower in JAM compared to controls (figures 10 and 11). The total number of voxels comprised in the clusters decreased over the different evaluations (Table 8) indicating that the local volume of the ROI in JAM was more similar to the healthy brain after the DP and the DP-LLR therapy phases. These results converge with the tractography volume analysis (see previous section). For the AF, the contrast Control > JAM also revealed different clusters showing lower volume lower in JAM compared to controls. However, contrary to the pattern found in the tractography analysis, here the cluster was bigger across the different evaluations (Table 9).

Table 8 | White matter voxel-based morphometry of the Frontal Aslant Tract in patient JAM at baseline and two endpoints compared to healthy control subjects.

		pFWE-corr	T	Peak Coordinates (MNI)			kE
FAT	Baseline	0.007	8.5	24	3	26	177
		0.018	7.89	36	-3	27	
		0.042	7.37	28	-4	33	
	Donepezil	0.005	8.74	28	-3	30	166
		0.007	8.54	26	6	21	
		0.024	7.73	36	-3	27	
	Donepezil + Therapy	0.006	8.66	32	2	26	160
		0.024	7.73	28	9	21	
		0.083	6.94	28	-3	33	
		0.024	7.73	28	9	21	

pFWE-corr indicates p Family Wise Error-corrected, T : t value, MNI: Montreal Neurological Institute, kE: cluster extent,

FAT : Frontal Aslant Tract.

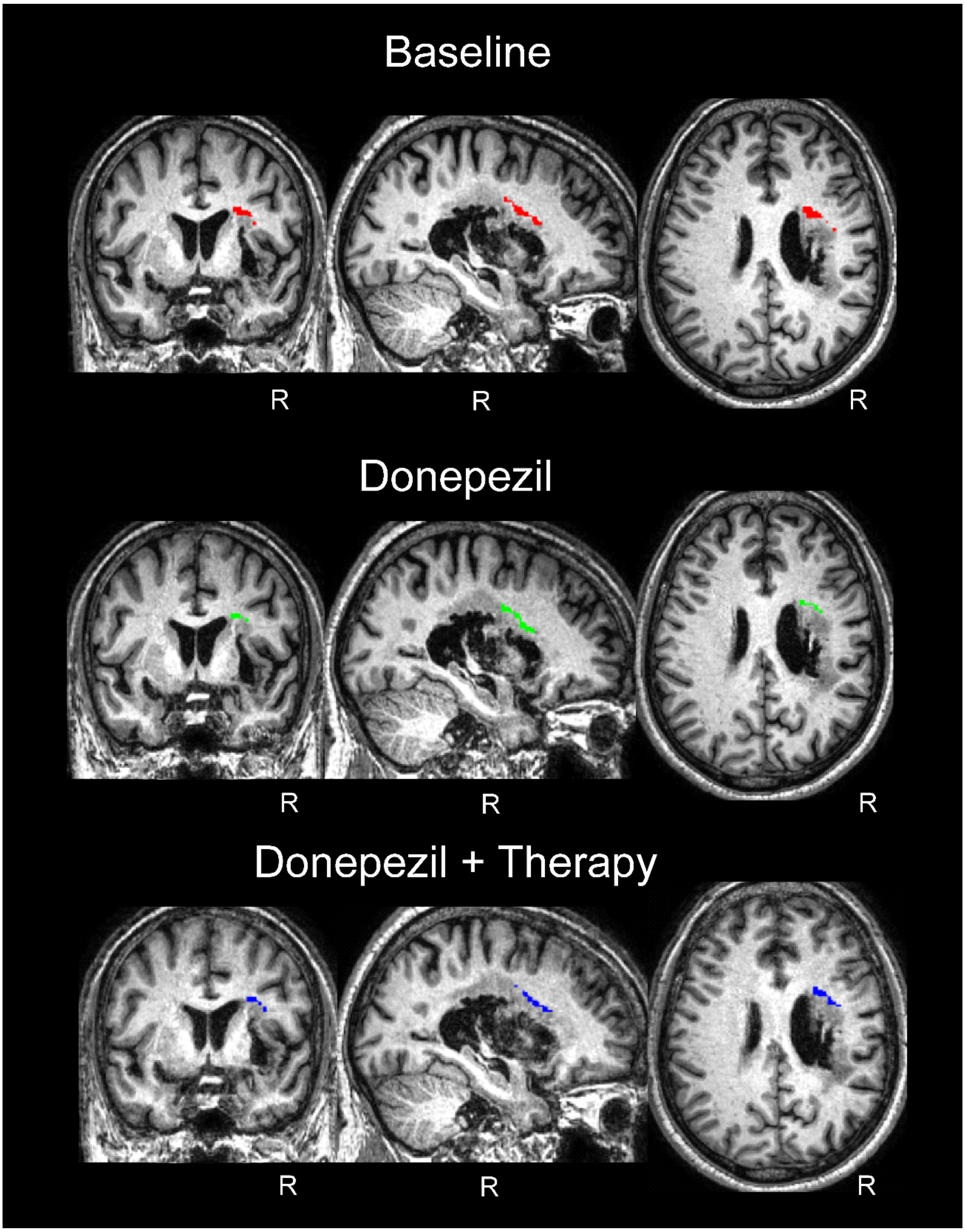

Figure 10. White matter voxel-based morphometry (VBM) results in the frontal aslant tract region of interest. Control group > Patient JAM: compared to patient JAM, the control group presented greater white matter volume in the region corresponding to the FAT in the right hemisphere. This difference decreases after the Donepezil phase, and after the Donepezil + therapy phases (see table X and results). No differences were found in the left hemisphere. Neurological convention is used. R: right.

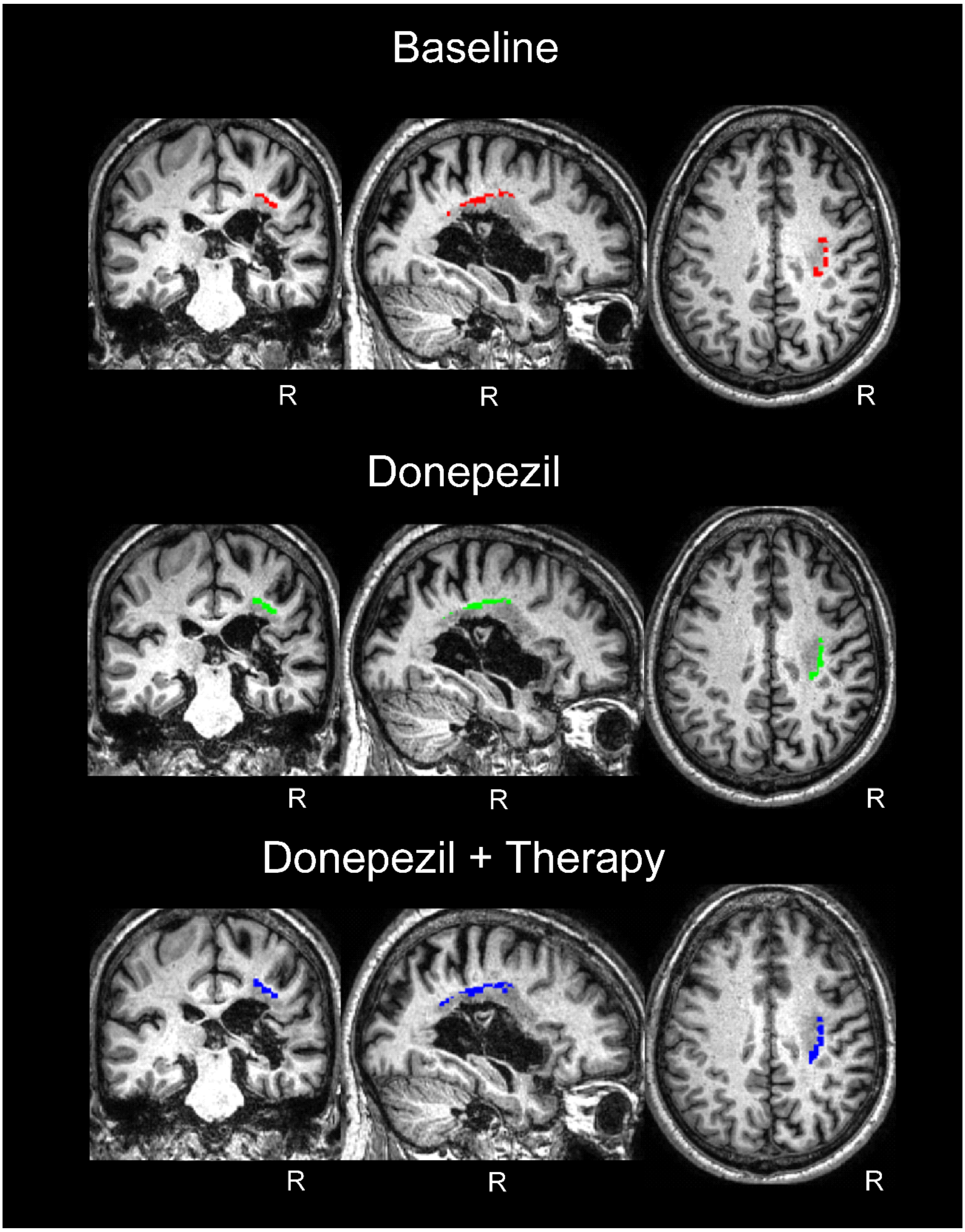

Figure 11. White matter voxel-based morphometry (VBM) results in the AF region of interest. Control group > Patient: compared to patient JAM, control group presented greater white matter volume in the region corresponding to the AF in the right hemisphere (see table X and results). No differences were found in the left hemisphere. Neurological convention is used. R: right.

Table 9 | White matter voxel-based morphometry of the AF in patient JAM at baseline and two endpoints compared to healthy control subjects.

		pFWE-corr	T	Peak Coordinates (MNI)			kE	Ke en AS/DS/PS
AF	Baseline	0.002	9.45	32	-24	33	212	206/189/0
		0.010	8.28	34	-14	33		
		0.021	7.81	28	-36	32		
		0.029	7.60	32	-15	38	38	36/27/0
		0.935	4.91	32	-6	36		
		0.065	7.09	36	-44	27	19	8/19/0
	Donepezil	0.003	9.15	32	-26	33	297	289/252/0
		0.020	7.85	34	-12	33		
		0.025	7.69	27	-34	33		
	Donepezil + Therapy	0.000	10.54	32	-12	33	306	297/265/0
		0.002	9.49	32	-30	32		
		0.003	9.05	28	-24	38		
		0.146	6.58	32	-46	27	16	8/15/0
		0.197	6.38	38	-42	30	13	12/13/0

pFWE-corr indicates p Family Wise Error-corrected, T : t value, MNI: Montreal Neurological Institute, kE: cluster extent, AF: Arcuate Fasciculus.

Discussion - Study 3

In the present study, treatment with DP alone and combined with LLR therapy improved aphasia severity, communication, and measures of speech fluency and repetition in JAM, a patient with crossed aphasia. The improvement ofa long-lasting language and communication deficits in JAM may be attributed to regional structural neuroplastic changes in the right FAT and DSAF. However, before advancing further in the interpretation of our results, data from JAM should be interpreted with caution because he had atypicalbrain-language organization (see De-Torres et al., 2013). JAM had both an atypical lateralization of language in the right hemisphere and a rare form of crossed aphasia (subcortical CA) (Alexander et al., 1989; Jung et al., 2010). These atypicalities prevent extrapolating the results obtained in JAM to other aphasic patients with typical lateralization and intrahemispheric organization of language functions in the left hemisphere. Moreover, since we studied a single case the causality of neuroplastic changes found with DTI in the right FAT and DSAFremains unclear. Finally, the open-label, uncontrolled design of our study is another limitation.

Despite these limitations, the present case study introduces new evidence to the few studies reporting the use of novel therapeutic interventions to treat crossed aphasia (Raymer et al., 2001; Jung et al., 2010; Lu et al., 2014). Until now, only three patients with chronic crossed aphasia have been treated with biological interventions (drugs and non-invasive brain stimulation). Raymer et al. (2001) treated apatient with transcortical motor aphasia with the dopamine agonist bromocriptine. Dopaminergic stimulation producedlong-lasting benefits in verbal fluency (words/minute in discourse), even after drug withdrawal, with little improvement in emotional prosody and gestural tasks. Language deficits in a patient with crossed aphasia were treated with inhibitory (1 Hz) rTMSover different cortical areas of the left hemisphere. The patient JAM had chronic CA secondary to a right basal ganglia haemorrhage (Jung et al., 2010). After a short trial of rTMS over the left parietal lobe, improvements in language were restricted to the naming subtest of the WAB (pre-rTMS: 54/100; post-rTMS: 64/100) with no changes in fluency (pre-rTMS: 11/20; post-rTMS: 11.5/20). Post-treatment fMRI showed significant activations in the right inferior frontal gyrus, posterior temporal gyrus, and parietal lobe for both the noun generation and sentence completion paradigms (Jung et al., 2010).

LANGUAGE AND COMMUNICATION

Treatments with DP alone and combined with LLR therapy in JAM improved aphasia severity (WAB-AQ) and deficits in everyday communication (CAL). This parallel improvement was not unexpected. In a previous study we demonstrated that a combined intervention with DP and conventional speech-language therapy in patients with chronic post-stroke aphasia and left hemisphere lesions significantly improved both domains (Berthier et al., 2006). Speech fluency and auditory comprehension subtests of the WAB showed improvement in JAM, which is agreement with the results of previous studies showing that gains after training repetition alone (for recent reviews see Salis et al., 2015; Eom and Sunga, 2016) and combined with drugs (Berthier et al., 2014) can generalize to other language domains. The improvement in everyday communication in JAM is relevant because deficits in everyday communication are strongly related to overall aphasia severity (Fucetola et al., 2006; Mazaux et al., 2013) and because recovery of spoken language in many aphasic patients rarely "scale up" from fragmented and paraphasic emissions to more cohesive and efficient everyday communication. It is important to mention that both interventions (DP and DP-LLR therapy) improved quality but not amount of everyday communication. This dissociation is reasonable because at baseline assessment JAM had fluent spontaneous speech (see next section), but the content of his emissions was contaminated by hesitation, some phonemic paraphasias, and occasional self-corrections (De-Torres et al., 2013). Therefore, there was more room for improvement in quality than for amount of communication. Although language and communication are inherently linked to convey a coordinate message during social interaction, these functions may be dissociable by virtue of depending on the activity of different cortical areas (Willems & Varley, 2011; Catani & Bambini, 2014). Spoken production depends on the activity of perisylvian areas, whereas the intention to communicate relies on the activity of the medial frontal cortex (pre-SMA, SMA, and anterior cingulate gyrus). Since these distant cortical areas are connected via the FAT (Catani et al., 2013; Hartwigsen et al., 2013), modeling the right FAT could have speeded the propagation of neural impulses between the medial frontal cortex important for modulating communicative intentions and the inferior frontal gyrus mediating spoken production.It was noteworthy that voxel-brain morphometry of cortical areas connected by these two white matter tracts showed no changes with either intervention.

SPEECH FLUENCY AND THE FRONTAL ASLANT TRACT

Treatment with DP alone in JAM improved the scores on the experimental measures of speech fluency (efficiency and speech rate). These gains slightly decreased with combined DP-LLR therapy and after ending both interventions, thus indicating that the drug alone provided the most noticeable effects. Note that JAM had a fluent aphasia obtaining a high score on speech fluency of the WAB

(8/10) in both baseline assessments, but the score on this subtest showed no significant changes improvement (9/10) throughout the trial. Although stability on this 10-point scale may reflect a ceiling effect, it is also possible that this metric has failed to capture changes (see Gordon, 1998).

Previous cross-sectional neuroimaging studies in aphasic patients with stroke (Marchina et al., 2011; Fridriksson et al., 2013; Wang et al., 2013; Basilakos et al., 2014) and degenerative conditions (Catani et al., 2013) as well as computational implementations (Roelofs, 2014) collectively suggest that the FAT and the ASAF play a synergistic role to support speech fluency during communication.In our longitudinal study of this single case, we foundincreased volume in the right FAT and reduction ofits volumetric difference relative to healthy controls (structural plasticity) with DP alone and DP combined with LLR therapy. By contrast, the right ASAFinstead showed a steady decrement in volumeand increased volumetric difference when compared with healthy controls throughout the trial. Thus, both interventions induced circumscribed structural plasticity in one white matter tract coupled with shrinkage of the other. These divergent changes arecomparable with the results of experimental studies in animals treated with psychoactive drugs, which showed not only that plastic changes are region-specific, but also that different regions can express opposite changes (see Kolb and Gibb, 2014; 2015). Moreover, the fact that the right FAT was anatomically intact can justify changes on its microstructure in response to pharmacological and behavioural manipulation, whereas detrimental changes in the ASAF probably resulted because it was involved in the lesion. Therefore, the shrinkage of the right ASAF in JAM cast doubts on its participation in the recovery of speech fluency. The role of the expansion of part of the area of tissue damage during the trial on inducing reductive changes in the ASAF is elusive because its topographical location was more superficial than the lesion. The left FAT and ASAF showed no relevant volume changes with either treatment.

REPETITION AND THE ARCUATE FASCICULUS

Repetition of words improved with both interventions (DP and DP-LLR therapy), whereas repetition of sentences from the PALPA test was very difficult to JAM and it did not improved at all with either treatment. Repetition of clichés and novel phrases only improved with the combined treatment and performance on clichès declined thereafter, but gains in repetition of novel sentences remained highly significant in the first posttreatment evaluation. Thus, treatment with DP alone exerted amodest priming effect for novel sentence repetition only, yet the addition of behavioral training significantly boosted performance in both tasks. The superior improvement of novel sentences as compared to matched idiomatic clichés aligns well with findings from cases of CA after left hemisphere strokes treated with a similar strategy (Berthier et al., 2014). Although treatment with DP alone and combined DP-LLR therapy were associated with steady volume increments of the right DSAF, a segment of the AF implicated in verbal repetition (Saur et al., 2008), these changes were not apparent when this tract was compared to those of healthy controls.This casts doubts about the role of the both interventions in harnessing plasticity in the right DSAF, but also these seemingly opposingfindings add weight to the role of the FAT inrepetition performance (Hartwigsen et al., 2013). The FAT was unrelated to repetition performance in primary progressive aphasia (Catani et al., 2013), but verbal repetition in healthy subjects increased the interaction of cortical areas (pre-SMA and dorsal premotor cortex) connected by the left FAT (Hartwigsen et al., 2013).

CANDIDATE MECHANISMS FOR STRUCTURAL PLASTICITY IN WHITE MATTER TRACTS

Comparisons of DTI data at pre- and post-treatment phases in JAM revealed local events of plasticityin theright FAT and DSAFwith no longitudinal plastic changes in the homologous tracts of the left hemisphere nor in the cerebral cortex connected by these tracts. Thus, it seems that cholinergic potentiation with DP alone primed selectively plastic changes in certain white mattertracts (FAT, DSAF) and the continued effectof this cholinergic agent acting in concert withrepetitive LLR therapyharnessed activity-dependent plasticity of these white matter tracts. The causal relationship between the observed plastic changes and cholinergic modulation is elusive, but it concurs with the results of different lines of research (Mesulam et al., 1992; 2003; Raghanti et al., 2008; Bohnen et al., 2009; Hiraoka et al., 2009; Imamura et al., 2015). Postmortem analysis of the human cholinergic system in the mesial frontal lobe (Brodmann area 32) (Raghanti et al., 2008), which is one of the anatomical origins of the FAT (Catani et al., 2013) and crucial for communicative intentions (Catani & Bambini, 2014), revealed dense clusters of cholinergic axons which probably represent local events of plasticity or circuitry rearrangement (Mesulam et al., 1992; Raghanti et al., 2008). An in vivo study using positron emission tomography (PET) and 1Cmethyl-4-piperidinyl propionate acetylcholinesterase (AChE) in middle-aged and elderly non-demented subjects with periventricular white matter involvement of vascular origin was associated with reduced cortical cholinergic activity most likely by an interruption of ascending cholinergic projections in the white matter (Bohnen et al., 2009). In complementary terms, a histochemical study of a young patient with pure subcortical vascular lesions disclosed disruption of the ascending cholinergic pathways in the deep white matter, although some acetylcholine-rich-fibers and cholinergic cortical neurons survived even in the areas of greatest cholinergic denervation (Mesulam et al., 2003). Moreover, knowledge on the brain sites of binding of DP is providing further insight. A study in healthy subjects using PET and [5-(11) C-methoxy]-donepezil showed a moderate concentration of the radiotracer in some cortical areas (frontal and anterior cingulate gyrus) which are the origins of the FAT (Hiraoka et al., 2009, Catani et al., 2013). Finally, in vitro studies showed that treatment with DP, via stimulation of nicotinic receptors, rapidly increase oligodentrocyte differentiation and myelination (Imamura et al., 2015).

In summary, we found that a neuroscientifically-based intervention with a cognitive enhancing drug and audiovisual repetition-imitation therapy improved chronic language and communication deficits in a patient with crossed aphasia. These beneficial changes were underpinned by highly focal plastic changes in white matter tracts in the lesioned hemisphere.

CONCLUSIONS

- In Study 1 we demonstrate for the first time that treatment combining Massed Sentence Repetition Training (MSRT) (40 hours in eight weeks) with donepezil (DP) was associated to better outcomes in speech production deficits than pairing DP with Distributed speech-language therapy (DSLT) (40 hours in 16 weeks). Although both types of interventions were effective to improve speech production deficits, MSRT combined with DP augmented and speed up the benefits provided by the more distributed therapy (DSLT). These findings demonstrate that intensive treatments are associated with better outcomes than traditional, non-intensive therapies. In addition, these findings suggest that combining a biological treatment (DP) with model-based interventions are promising strategies to treat post-stroke aphasia.
- To implement a similar therapeutic intervention than in Study 1, we evaluated a patient (JAM) with chronic post-stroke conduction aphasia (CA) with the aim of establishing a comprehensive baseline assessment in Study 2. We did find stable language and communication deficits. Language deficits mainly affected repetition and the profile of these deficits was atypical reflecting a reduced interaction between phonological and lexical semantic systems. This finding suggests that the interaction between both cerebral hemispheres in patients with crossed aphasia is atypical.
- In Study 3, the model-based intervention using a cognitive enhancing drug (DP) and audiovisual repetition-imitation therapy in patient JAM improved language and communication deficits. These beneficial changes were underpinned by highly focal plastic changes in right white matter tracts (frontal aslant tract [FAT] and right direct segment of arcuate fasciculus [DSAF]). We

did not find structural plasticity in grey matter area interconnected by these tracts nor in the left hemisphere.

Conclusiones

- En el estudio 1 se demuestra, por primera vez, que el tratamiento combinando el entrenamiento intensivo de repetición de oraciones (MSRT) (40 horas en ocho semanas) con donepezilo (DP) asocia mejores resultados en los déficits de producción de habla que los que se obtienen con el tratamiento combinado de DP y terapia del habla menos intensiva (DSLT) (40 horas en 16 semanas). Aunque ambos tipos de intervenciones fueron eficaces para mejorar los déficits de producción de habla, MSRT combinado con DP aumentó y aceleró los beneficios proporcionados por la terapia más extendida en el tiempo (DSLT). Estos hallazgos demuestran que los tratamientos intensivos están asociados con mejores resultados que las terapias tradicionales, no intensivas. Además, estos hallazgos sugieren que la combinación de un tratamiento biológico (DP) con intervenciones basadas en modelos son estrategias prometedoras para el tratamiento de la afasia post-ictus.
- Para implementar una intervención terapéutica similar a la del Estudio 1, se evaluó a un paciente (JAM) con afasia de conducción crónica post-ictus con el objetivo de establecer una evaluación basal completa (Estudio 2). Encontramos deficiencias de lenguaje y comunicación estabilizadas. Los déficits de lenguaje afectaron principalmente a la repetición y el perfil de estos déficits fue atípico, lo que refleja una menor interacción entre los sistemas semánticos, fonológicos y léxicos. Este hallazgo sugiere que la interacción entre ambos hemisferios cerebrales en pacientes con afasia cruzada es atípica.

- La intervención basada en modelos utilizando un fármaco (DP) y la terapia de imitación repetitiva con apoyo audiovisual en el paciente JAM mejoró los déficits de lenguaje y comunicación (Estudio 3). Estos cambios positivos fueron apoyados por cambios plásticos altamente focales en los tractos de la sustancia blanca derecha (tracto aslant frontal y segmento directo del fascículo arcuato derecho). No encontramos plasticidad estructural en el área de materia gris interconectada por estos tractos ni en el hemisferio izquierdo.

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