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Neural mechanisms of high-level cognitive processes in task preparation and implementation

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INTRODUCCIÓN

Una de las características por excelencia de los seres humanos es la capacidad de guiar nuestro comportamiento en base a nuestros objetivos. Esto nos permite, en primer lugar, responder eficientemente a las demandas del entorno y, consecuentemente, adaptarnos de forma eficaz a contextos nuevos con los que no tenemos experiencia previa. Esta tesis busca avanzar nuestro conocimiento acerca de cómo estos procesos de *control* interactúan con otros procesos relacionados, y cómo son implementados en nuestro cerebro.

Formalmente, el control cognitivo (o *control*, en adelante) hace referencia a aquellos procesos que nos permiten actuar en base a metas, sesgando la competición de planes de acción de acuerdo con nuestros objetivos (Norman & Shallice, 1980). Como problema central de nuestra cognición, el control ganó rápidamente atención en el campo de la ciencia cognitiva, viéndose ligado al procesamiento consciente y al esfuerzo subjetivo. Durante estos años, diferentes tareas como la tarea Stroop (Stroop, 1935), Simon (Simon, 1969), o de flancos (Eriksen & Eriksen, 1974), así como multitud de modificaciones de las anteriores (Egner, 2008), han ayudado a caracterizar los procesos de control. A nivel cerebral, los primeros estudios en el campo utilizaron pacientes con déficits ejecutivos para asociar la corteza prefrontal con estos procesos (Luria, 1966). Con el advenimiento de las técnicas de neuroimagen, el incremento significativo de investigación ha puesto de manifiesto el importante rol de diferentes zonas más allá de la corteza prefrontal (Duncan, 2010; Petersen & Posner, 2012), así como la existencia de redes que funcionan en distintas escalas temporales (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008). Por otro lado, en estos años, se han propuesto influyentes modelos de competición sesgada, según los cuales una fuente (por ejemplo, la corteza prefrontal) sesga representaciones relevantes para la tarea en regiones específicas, de naturaleza más modular (Duncan, 2001).

Como mecanismo fundamental de regulación de nuestra actividad cognitiva, el control abarca multitud de fenómenos, pudiendo ser analizado en diferentes dimensiones y en relación con procesos relacionados pero disociables. Una de las dimensiones en las que puede ser analizado el control es la temporal. En este contexto, la tesis se articula en torno a una serie de preguntas asociadas al control aplicado de manera proactiva.

Los procesos de control pueden ser ejercidos de modo reactivo, esto es, de manera inmediata a la detección de un conflicto. Por otro lado, los procesos proactivos harían referencia a los mecanismos de ajuste que se producen al anticipar una situación demandante (Braver, 2012). El objetivo principal de este trabajo de tesis es avanzar nuestro conocimiento sobre dicho control proactivo. Para ello, en primer lugar, se analizó la relación de procesos de preparación con la consciencia de las instrucciones de tarea. En este sentido, algunos trabajos apuntan a que cierto sesgo en la selección de diferentes esquemas de acción puede conseguirse de forma inconsciente (e.g. Reuss, Kiesel, Kunde, & Hommel, 2011). Sin embargo, otros estudios sugieren la necesidad de experiencia consciente para ejercer control proactivo (Kiefer, Adams, & Zovko, 2012; Kiefer & Martens, 2010). Como primera parte de esta tesis, se llevó a cabo una serie de experimentos comportamentales con el objetivo de intentar resolver esta diatriba.

En segundo lugar, se estudió la capacidad de una de las técnicas de neuroimagen más extendidas, la resonancia magnética funcional (*fMRI*, por sus siglas en inglés), para estudiar la implementación neural de procesos cognitivos. Debido a que el papel de esta técnica en el estudio de procesos y funciones cognitivas no está exento de polémicas y críticas, y debido también al peso de la *fMRI* en los experimentos de esta tesis, un objetivo fue, por tanto, la realización, de manera previa a los experimentos, de una revisión de los consideraciones más relevantes en este sentido.

De los mecanismos asociados al control proactivo, la preparación, entendida como el ajuste a las reglas de tarea que se produce antes de que aparezca el estímulo objetivo (Rogers & Monsell, 1995), es posiblemente uno de los que más atención ha recibido. En el laboratorio, esta preparación se elicita por medio de señales o claves que indican al sujeto las demandas que serán requeridas a continuación. A nivel neural, el análisis de las respuestas cerebrales ante estas claves ha permitido identificar una serie de zonas que parecen estar especialmente involucradas en el control proactivo. Otras zonas parecen estar relacionadas con el procesamiento de aspectos específicos de la tarea. Sin embargo, en estos experimentos la interferencia entre tareas es una gran fuente de confundidos. Teniendo en cuenta, por tanto, que no existe una respuesta inequívoca respecto a si la preparación en contextos de baja interferencia es general o específica, uno de los objetivos de este trabajo consistió en utilizar *fMRI* para contestar a esta pregunta.

La mayoría de estudios de preparación han utilizado paradigmas que se centran en situaciones repetitivas. Sin embargo, la demanda de control se asume mayor en situaciones novedosas en las que se ha de generar un nuevo esquema de acción (Norman & Shallice, 1980). Qué ocurre durante el período de preparación de situaciones complejas y novedosas es una pregunta que, a pesar de ello, ha recibido significativamente menos atención (Cole, Laurent, & Stocco, 2013). Por tanto, otro objetivo de esta tesis fue la evaluación de los procesos neurales subyacentes a la implementación de instrucciones verbales, al requerir estas la creación y ejecución de esquemas de acción novedosos.

En esta introducción, se describirán en profundidad el contexto en el que se enmarca así como las problemáticas concretas que se pretenden abordar en esta tesis. Posteriormente, se especificarán los objetivos concretos perseguidos.

1. Definición de control cognitivo: mecanismos reactivos y proactivos

Pese a que su conceptualización, así como la mera existencia de un mecanismo de este tipo, fueron objeto de debate desde principios del Siglo XX, los procesos de control vuelven a ganar atención con la llegada de la metáfora de la mente como ordenador, a partir de la cual la cognición humana es concebida como un sistema de procesamiento de la información. En este contexto, Atkinson y Shiffrin (1968) proponen la existencia de procesos de control lábiles, en contraposición a procesos aprendidos o inherentes a nuestra estructura de procesamiento. La distinción, descrita generalmente como modos de procesamiento automático o controlado, fue desarrollada más adelante por Posner y Snyder (1975). Según los autores, un proceso automático es aquel que ocurre sin intención, sin experiencia consciente y sin interferir en el resto de actividad mental, mientras que los procesos controlados están asociados a un sistema de capacidad limitada. Los autores proponen además la existencia de un mecanismo (igualmente de capacidad limitada) que, más que saturarse, se dirige hacia un tipo de información, un canal de *inputs*, o una respuesta determinados en función de estrategias conscientes. En este contexto, Posner y Snyder (1975) emplean el término control cognitivo para hacer referencia al mecanismo que permite implementar conscientemente programas de operaciones concretos (también denominados estrategias) al recibir una información determinada.

Formalmente, por tanto, el control puede ser definido como un mecanismo que regula el pensamiento y el comportamiento del sujeto en base a representaciones internas de sus metas (Braver, 2012), mediante la selección de esquemas de acción asociados a las mismas. De entre los diferentes modelos que intentan explicar cómo se llevan a cabo estos procesos de control, destaca especialmente el de Norman y Shallice (1980). Los autores postulan la existencia de dos mecanismos: un programador de esquemas competitivos (*content scheduling*) y el sistema atencional supervisor. Mientras que el *content scheduling* se encargaría de coordinar aquellos esquemas de acción automáticos, basados en rutinas familiares, el sistema atencional supervisor *sesga la competición* entre diferentes elementos de entrada cuando los esquemas de acción automáticos no son suficientes para hacer frente a la situación. De forma similar, en el modelo de memoria de Baddeley (1992), una suerte de sistema atencional supervisor, denominado por el autor como "ejecutivo central", manipularía la información almacenada en el sistema de memoria a corto plazo en base a metas y objetivos.

Inherente a estos modelos y definiciones de control es la idea de que este ejerce su influencia sobre multitud de contextos, situaciones, y dominios de estimulación. Igualmente, esta influencia puede ser estudiada desde varias perspectivas. Esto ha motivado la creación de diversas taxonomías y esquemas teóricos acerca de los diferentes tipos de control. De las múltiples dimensiones en las que el control puede ser analizado, en este trabajo nos centramos en la temporal. Esta dimensión nos permite distinguir entre dos grandes maneras de ejercer control: proactiva y reactiva. De acuerdo con Braver (2012), el control reactivo hace referencia a un mecanismo que "depende de la detección y resolución de la interferencia en el momento en el que esta ocurre". Por lo tanto, el control reactivo juega un rol de "corrección tardía", reclutado únicamente cuando es estrictamente necesario para resolver la interferencia. En contraposición, el control proactivo se define como un mecanismo de anticipación a situaciones demandantes que "mantiene de forma activa y sostenida información relevante para las metas" del sujeto. Este mantenimiento de información relevante de forma anticipatoria ejerce una influencia acorde con los objetivos del sujeto sobre los sistemas de atención, percepción y acción involucrados en situaciones que requieren control. Por lo tanto, el control proactivo "depende de la anticipación y prevención de la interferencia antes de que esta ocurra".

De acuerdo con el objetivo principal de este trabajo, en el resto de la introducción nos centraremos exclusivamente en aquellos aspectos concernientes al control proactivo. Concretamente, en el siguiente apartado pretendemos contextualizar la introducción en el marco de aquellos dominios de control proactivo relevantes para nuestros objetivos.

2. Funciones del control proactivo: su papel en los sets mentales

Pese a que el control, en general, puede ejercer su influencia sobre diversos dominios (Klein & Lawrence, 2012), el control proactivo se encuentra íntimamente relacionado con los esquemas mentales de tarea (a partir de ahora, sets de tarea). Formalmente, el set de tarea es la representación mental de un plan de acción generado a partir de las metas del sujeto y que contiene una serie de reglas concretas que permiten su ejecución (Rubinstein, Meyer, & Evans, 2001). De acuerdo a esta definición, la relación entre control proactivo y set de tarea se hace evidente tanto en situaciones de nuestra vida diaria (por ejemplo, cuando elegimos la ruta más rápida para llegar a nuestro lugar de trabajo) como en el laboratorio. En este caso, el paradigma empleado habitualmente utiliza claves que señalan qué tipo de tarea se ha de realizar a continuación (Monsell, 2003).

En este tipo de paradigma, el proceso conocido como preparación ha suscitado un interés considerable. Podemos entender la preparación como el ajuste a las reglas de tarea que se produce antes de que aparezca el estímulo objetivo (Rogers & Monsell, 1995). Así, el proceso de preparación se elicita al presentar señales que indican que tarea se ha de realizar a continuación, permitendo al participante llevar a cabo la necesaria reconfiguración del esquema mental (Meiran, 1996; Rogers & Monsell, 1995). Esta reconfiguración puede incluir diferentes fenómenos, tales como fijar la atención en una atributo diferente del estímulo (por ejemplo, del significado de la palabra a la percepción del número de vocales de esa palabra) o actualizar el mapeo estímulo-respuesta (Monsell, 2003). Generalmente, se asume que la reconfiguración del set de tarea incluye dos componentes principales, la activación de la meta y la activación de la regla (Meiran, Chorev, & Sapir, 2000).

A continuación, evaluaremos la relación del control proactivo con otro proceso íntimamente relacionado, como es la consciencia. De lo presentado hasta ahora se desprende la conclusión de que generalmente el control proactivo se ejerce en situaciones que requieren la integración de un considerable número de elementos. La consciencia, cuya función generalmente se asocia con la integración de información (Baars, 1997; Koch, 2004), ha estado por tanto tradicionalmente asociada a los procesos de control (Norman & Shallice, 1980; Posner & Snyder, 1975). La relación entre ambos procesos es discutida en detalle a continuación.

3. Control proactivo y consciencia

Basándonos en la definición de control proactivo que venimos trabajando, el control *per se* no necesita de experiencia consciente asociada para ejercer su influencia. En otras palabras, el "control no requiere de un meta-conocimiento acerca de cuándo y cómo aplicarlo" (Kunde, Reuss, & Kiesel, 2012). Por ejemplo, no tendría sentido decir que uno es consciente del funcionamiento de su memoria de trabajo, sino de las consecuencias de este, como por ejemplo, la retención de información relevante en el tiempo. Por lo tanto, una opción transparente a nivel teórico es catalogar a este tipo de fenómenos como procesos de control asociados a experiencias conscientes. Pese a ello, es cierto que control y consciencia se encuentran *intuitivamente* ligados en los modelos teóricos predominantes. De forma ilustrativa, las influyentes propuestas de Posner y Snyder (1975) o Norman y Shallice (1980) asocian control a consciencia explícitamente. Quedaría responder, por tanto, qué rol juega la consciencia para que esta asociación se produzca de forma tan habitual.

Un primer acercamiento para evaluar el papel de la consciencia en el control proactivo es estudiar hasta qué punto esta es necesaria para que se dé tal proceso de control. Importantes teorías de consciencia no descartan la posibilidad de que funciones cognitivas superiores sean sensibles a otros formatos de información que escapen a nuestra experiencia subjetiva consciente (Lau & Passingham, 2007). Esto abre la puerta a que, igualmente, los mecanismos de preparación o el control proactivo en general se vean influidos por información inconsciente. La respuesta a esta pregunta va a depender, en primer lugar, de la propia definición de procesamiento subliminal, cuya elección no está exenta de polémica (Hannula, Simons, & Cohen, 2005; Holender, 1986; Mattler, 2003; van Gaal, de Lange, & Cohen, 2012). Así, si nos basamos en un umbral objetivo de consciencia, se considera un estímulo subliminal exclusivamente cuando los participantes son incapaces de detectarlo, en términos de Teoría de Detección de Señales. Por el contrario, un umbral subjetivo utiliza únicamente el reporte subjetivo de los participantes como medida de consciencia. Cuando se emplea este umbral, un estímulo es considerado no consciente cuando el participante es incapaz de reportar la percepción del mismo, aun cuando pueda detectar el estímulo objetivamente (Merikle, Smilek, & Eastwood, 2001). Pese a que este umbral es menos estricto, es más coherente con ciertos modelos explicativos (Snodgrass & Shevrin, 2006) y los planteamientos teóricos (Lau & Rosenthal, 2011) utilizados en esta tesis.

Más allá de la definición de percepción subliminal, el marco teórico elegido va a condicionar también la respuesta a la pregunta de si información inconsciente puede afectar al control proactivo. En este sentido, las propuestas de las Teorías de Orden Superior (Lau & Rosenthal, 2011) son coherentes con la idea de que no existe control consciente como tal sino consciencia de los resultados del mismo (Hommel, 2017). A diferencia de otros modelos de gran potencia explicativa como el Espacio neuronal global de trabajo (Dehaene & Changeux, 2011; Dehaene & Naccache, 2001), las Teorías de orden superior (Lau & Rosenthal, 2011) proponen la disociación entre consciencia y otros procesos de alto nivel que permiten una ejecución exitosa (tales como atención, memoria o control). Las Teorías de orden superior plantean que la experiencia consciente es el colofón a una cadena jerárquica de procesos, en la que la ejecución de la tarea (y los mecanismos de control asociados) se situaría en un paso previo e independiente a la consciencia de la misma. Dicho de otro modo, esta visión no asume la asociación entre consciencia y la capacidad de ejecución, sino que plantea que la consciencia funciona como un sistema de monitorización tardío, el cual funcionaría bajo sus propios principios, con independencia de la eficacia de nuestra ejecución, la cual depende a su vez de procesos como la atención o el control (Lau & Rosenthal, 2011). De forma relacionada, y en relación al uso de un umbral objetivo o subjetivo, estas teorías defienden que cuando utilizamos un umbral objetivo lo hacemos a costa de degradar enormemente la señal del estímulo. Esto impide saber si el habitual peor rendimiento de los sujetos con estos estímulos subliminales se debe a una falta de consciencia sobre los mismos o, por el contrario, a la propia degradación de la señal a nivel perceptivo (Lau & Rosenthal, 2011). Pese a que, por tanto, la utilización de un umbral objetivo estaría condicionando las conclusiones, diversos estudios han encontrado resultados a favor de la influencia inconsciente en procesos de alto nivel incluso utilizando este estricto criterio (Kunde et al., 2012; Lau & Passingham, 2007; van Gaal et al., 2012).

Hasta ahora hemos defendido un argumento acerca de cómo la información inconsciente podría influir en los procesos de control. Sin embargo, diversa evidencia pone de manifiesto que la eficacia de nuestro comportamiento a la hora de llevar a cabo una tarea determinada va a depender tanto de nuestras intenciones y metas, como de cómo esté configurado el contexto (Monsell, 2003). En este sentido, Hommel (2007, 2017) propone que la consciencia jugaría un papel integrador de información de diversa procedencia para facilitar la actuación de los mecanismos de control. En tanto en cuanto la consciencia se entiende como un mecanismo asociado a la integración de información dispar (Baars, 1997; Koch, 2004), Hommel (2017) plantea que la experiencia consciente estaría ligada a procesos con alta carga de información, como la implementación de objetivos o la resolución de conflictos. En esta línea, diversos estudios han puesto de manifiesto cómo la influencia de información inconsciente depende de una configuración consciente del contexto (Kiefer, 2007, 2012; Kiefer et al., 2012; Kiefer & Martens, 2010). El efecto de esta configuración consciente en los procesos de preparación es desconocido.

4. Bases neurales del control proactivo

En paralelo al desarrollo teórico de los conceptos discutidos en el apartado anterior, la aparición y posterior perfeccionamiento de diversas técnicas de neuroimagen han permitido un progresivo avance en la búsqueda de los correlatos neurales del control proactivo. De acuerdo con la evidencia clásica acerca de una especialización funcional de diferentes zonas cerebrales, la corteza prefrontal es considerada una zona crucial en la representación y mantenimiento del set de tarea en situaciones preparatorias (Sakai, 2008). Sus características citoarquitectónicas parecen subyacer a este papel central en el control proactivo. Por ejemplo, su naturaleza transmodal permite su implicación en el procesamiento de modalidades de información muy dispares (Mesulam, 1998; Miller & Cohen, 2001). Además, la cantidad de vías de retroalimentación que proyectan desde la corteza prefrontal a prácticamente el resto del cerebro permiten la modulación del procesamiento en regiones posteriores en base a metas y objetivos representados en esta zona (Miller & Cohen, 2001). Más allá de estos principios organizativos comunes, la corteza prefrontal parece poder subdividirse en diferentes regiones de acuerdo a la función que desempeñan. En este sentido, diferentes modelos sugieren la existencia de un gradiente de abstracción caudal-rostral, en el cual aspectos más concretos del set de tarea se representan en regiones más posteriores mientras que los aspectos más abstractos lo hacen en zonas anteriores de la corteza (Badre & D'Esposito, 2007; Koechlin, Ody, & Kouneiher, 2003). De esta manera, regiones de la corteza prefrontal lateral estarían a la base de la actualización del set de tarea (Brass & von Cramon, 2002, 2004) y la integración del mapeo estímulo-respuesta con la meta de la tarea (Brass & von Cramon, 2004). Por el contrario, regiones más anteriores, como la corteza prefrontal anterior, representarían aspectos más abstractos como estrategias e intenciones (Gilbert, 2011; Haynes, 2011).

Dos regiones de la corteza parietal parecen jugar también un papel importante en el control proactivo sobre el set de tarea. Por un lado, el lóbulo parietal inferior se encuentra implicado en la integración sensorio-motora, mediante la representación de mapeos estímulo-respuesta. Por ejemplo, al inhibir esta región mediante estimulación magnética transcraneal se impide la actualización del mapeo asociado al set de tarea (Muhle-Karbe, Andres, & Brass, 2014). Por otro lado, el lóbulo parietal superior parece estar involucrado en la activación y manipulación de las representaciones de las reglas vinculadas al set de tarea (De Baene & Brass, 2014).

Adicionalmente, otra región habitualmente implicada en este tipo de paradigma es la corteza premotora suplementaria. Esta región parece subyacer a la supresión de la interferencia proveniente de otros sets de tarea relevantes durante el período de preparación (Crone, Wendelken, Donohue, & Bunge, 2006; De Baene & Brass, 2014).

La relevancia en situaciones de control de las regiones mencionadas hasta ahora, en conjunción con otras como la ínsula anterior y la corteza cingulada anterior, es recogida por influyentes modelos, tales como el modelo de Red de Múltiple Demanda (Duncan, 2010). De acuerdo a este modelo, estas regiones formarían una red que subyacería al establecimiento y control de programas mentales en situaciones que requieren la integración de demandas diversas y la descomposición de problemas en sub-tareas. Algunas de estas zonas, concretamente las regiones frontoparietales, parecen estar más involucradas en un control de tipo fásico, permitiendo el establecimiento y ajuste inicial de control. Por el contrario, la ínsula anterior y la corteza cingulada anterior parecen estar a la base de un control sostenido en largos lapsos de tiempo (Dosenbach et al., 2008). Pese a que esto podría sugerir una mayor implicación de estas regiones en control proactivo, no existe evidencia para diferenciarlas inequívocamente de regiones frontoparietales en este sentido (Palenciano, Díaz-Gutiérrez, González-García, & Ruz, *en prensa*).

Por último, recientes trabajos defienden la relación de estas áreas con regiones subcorticales. Por ejemplo, Buschman y Miller (2014) proponen que la interacción entre corteza prefrontal y los ganglios basales subyacería a la generación de sets de tarea complejos. En esta interacción, el núcleo caudado y el putamen recibirían proyecciones de la corteza prefrontal, mientras que el globo pálido y la sustancia negra proyectarían de nuevo hacia zonas frontales a través de otras regiones, como el tálamo.

Hasta ahora nos hemos centrado en la descripción funcional de aquellas zonas que parecen ejercer un papel activo en los mecanismos de control proactivo. De acuerdo con los objetivos de este trabajo, a continuación, pasamos a describir los efectos de estos mecanismos, conocidos habitualmente con el nombre de efectos arriba-abajo (a partir de ahora, *top-down*), sobre otras regiones cerebrales.

4.1. Influencias *top-down* en procesos de alto nivel

En el contexto del estudio de los sets de tarea, el efecto *top-down* de zonas frontales sobre zonas de procesamiento selectivo o unimodal también ha sido puesto de manifiesto. Por ejemplo, Sakai y Passingham (2003) presentaban a los participantes un estímulo objetivo que podía ser procesado en términos espaciales o verbales. Para permitir la preparación de la tarea, con varios segundos de antelación mostraban a los participantes una señal con la información acerca de la tarea que tendrían que realizar a continuación. Los autores encontraron activaciones específicas para cada tarea en diferentes zonas del cerebro: el surco frontal superior y el lóbulo parietal superior en la tarea espacial, y el giro frontal inferior izquierdo y el giro temporal superior en la tarea verbal. Estas activaciones se producían tan pronto como la señal informativa era presentada, esto es, antes de que apareciese el estímulo objetivo. Una zona adicional, la corteza prefrontal anterior también se veía involucrada de manera prospectiva. Sin embargo, la implicación de esta zona era independiente de la tarea a realizar, es decir, común a la tarea espacial y verbal, sugiriendo la importancia de esta región en la representación del set de tarea. En un estudio posterior (Sakai & Passingham, 2006), estos autores demostraron que la implicación de esta región durante la presentación de la señal permitía predecir la eficacia en la ejecución de la tarea posterior. Igualmente, la actividad en esta región predecía también la actividad en zonas posteriores asociadas específicamente al tipo de tarea a realizar (semántica o espacial).

Hasta ahora, nos hemos centrado en un tipo de paradigma que se basa en la alternancia entre dos tareas altamente entrenadas (por ejemplo, una tarea semántica y una espacial). Aunque este paradigma nos permite caracterizar en parte los mecanismos de preparación, hay ciertos aspectos que quedarían inexplorados. Por ejemplo, una de las características esenciales del control cognitivo es que permite una adaptación rápida y eficaz a situaciones cambiantes y/o novedosas (Norman & Shallice, 1980). Diversos estudios han tratado de evaluar qué ocurre en estos contextos de alta novedad mediante la utilización de instrucciones verbales. En este tipo de estudios un mayor grado de control ha de ser ejercido ya que, a diferencia de los estudios clásicos en los que una señal indica qué tarea (de entre las practicadas con anterioridad) va a tener que realizarse, un nuevo set ha de ser creado e implementado en cada ensayo (Cole et al., 2013). Investigaciones con resonancia magnética funcional han revelado que activaciones frontoparietales subyacen también a la preparación (Hartstra, Kühn, Verguts, & Brass, 2011; Hartstra, Waszak, & Brass, 2012) e implementación (Cole, Bagic, Kass, & Schneider, 2010; Ruge & Wolfensteller, 2010) de este tipo de tarea. Sin embargo, el efecto de influencias *top-down* en el procesamiento de la información en estos contextos novedosos es menos conocido.

OBJETIVOS

En la introducción hemos descrito parte del extenso número de fenómenos en los que el control proactivo se ve envuelto. Con la intención de acotar el campo de estudio, este trabajo de tesis intentar arrojar luz sobre el control ejercido sobre sets de tarea. Concretamente, el principal objetivo de esta tesis es el estudio de su dependencia de la consciencia y la selectividad de las representaciones neurales asociadas al mismo. Para perseguir este objetivo, en primer lugar, evaluamos la relación del control proactivo con la experiencia subjetiva y con estrategias conscientes en una serie de experimentos comportamentales. Posteriormente, debido a la predominancia del uso de *fMRI* en este trabajo, determinamos en profundidad la utilidad teórica y consideraciones en el empleo de esta técnica en el estudio de fenómenos cognitivos. Por último, en dos experimentos con *fMRI* estudiamos los índices neurales de control proactivo en contextos de baja interferencia y de novedad de tareas.

1. *Set* de tarea y consciencia: Serie Experimental I

En los últimos años, diferentes estudios han mostrado influencias inconscientes en procesos de alto nivel. De especial importancia para este trabajo de tesis son los estudios que demuestran cómo información subliminal puede llegar a sesgar en ciertas situaciones la selección de un *set* de tarea por encima de otro. La Serie Experimental I de esta tesis se llevó a cabo con el objetivo, en primer lugar, de replicar resultados previos con un paradigma que tuviera en cuenta confundidos presentes en estos estudios para evaluar adecuadamente la existencia de un sesgo inconsciente en la selección de *sets de tarea*. Por otro lado, diversos estudios muestran que los efectos inconscientes observados en algunos procesos solo se producen bajo ciertas configuraciones de nuestros sistemas atencionales y de control. Sin embargo, la relación entre la configuración de nuestros sistemas de control y el efecto de información inconsciente en la selección del set de tarea no ha sido todavía explorada. Este objetivo es crucial para el trabajo de esta tesis, ya que su respuesta aportaría nueva información acerca de la relación entre consciencia y control cognitivo.

Por último, un objetivo adicional consistía en observar las semejanzas y las diferencias entre los umbrales objetivo y subjetivo de consciencia. Este objetivo a su vez se puede descomponer en dos sub-metas: estudiar el efecto de estímulos bajo el umbral subjetivo de consciencia en la selección del *set* de tarea, en el cual la degradación de la señal perceptiva de los estímulos es escasa; y evaluar la influencia del *set* ejecutivo sobre el efecto de estímulos bajo este umbral. En este caso, hipotetizamos que la representación de los estímulos a nivel perceptivo sería lo suficientemente adecuada como para que el procesamiento de los mismos no se viera afectado con la misma intensidad por representaciones de alto nivel basadas en metas y objetivos.

2. Resonancia magnética funcional y cognición: Revisión I

Dado el objetivo de evaluar los correlatos neurales del control cognitivo sobre *sets* mentales, gran parte del trabajo de esta tesis se basa en técnicas de neuroimagen, concretamente imágenes de *fMRI*. Sin embargo, el uso de esta técnica en este contexto, y en el de la psicología experimental en general, está sujeto a ciertas limitaciones, desde una perspectiva optimista, y a diversas críticas, desde una visión menos benevolente. Más allá de estas discutibles críticas, la propia técnica en la que se basa la resonancia magnética, así como la naturaleza de los datos obtenidos, demandan ciertas cautelas que, en ciertas ocasiones, no son tenidas en cuenta. Por tanto, el objetivo de este trabajo de revisión consistió en intentar agrupar estas críticas o limitaciones vertidas sobre el uso de resonancia magnética en ciencia cognitiva. Para facilitar su entendimiento, éstas fueron abordadas desde tres grandes perspectivas: técnica, estadística y teórica.

3. Índices neurales de control proactivo sobre *sets* mentales: Experimento I

En la introducción hemos mencionado algunos estudios acerca de los correlatos neurales de los efectos *top-down* sobre diferentes procesos cognitivos. En el campo del set de tarea, diversos estudios muestran que algunas zonas requeridas por una tarea concreta son reclutadas con antelación mediante la presentación de una señal informativa al respecto. Otros estudios, sin embargo, reportan la ausencia de especificidad preparatoria. La gran mayoría de estudios de neuroimagen acerca de efectos *top-down* sobre el set de tarea utilizan un paradigma en el que una clave señala la tarea a realizar. Este paradigma habitualmente se basa en la alternancia entre dos tareas. Por ello, la gran mayoría de estudios emplean tareas donde existe un alto grado de interferencia por distintos motivos. Esto es un aspecto importante, debido a que la interferencia supone un importante confundido al requerir una mayor involucración de recursos de control. Por tanto, el Experimento I de esta tesis consistió en un experimento de resonancia magnética funcional en el que los participantes realizaron una modificación de la tarea clásica empleada para evaluar los procesos de preparación. Esta tarea fue ajustada para estudiar de forma óptima los índices neurales de preparación en un contexto libre de interferencia. El objetivo de este estudio fue arrojar información acerca de la función de los mecanismos *top-down* asociados a los sets de tarea.

4. Índices neurales de control proactivo en situaciones novedosas: Experimento II

Por otro lado, como hemos mencionado en la introducción, el control cognitivo es de especial importancia en situaciones novedosas, complejas y/o inesperadas. En este sentido, el paradigma usado habitualmente (descrito en el Objetivo 3) tiene ciertas limitaciones ya que requiere que ambos sets de tarea hayan sido codificados previamente. Este paradigma, por tanto, no permite estudiar los efectos *top-down* asociados a *sets* de tarea en situaciones novedosas, pese a que estas no sólo son ecológicamente más cercanas a nuestro día a día, sino que teóricamente parecen estar más ligadas a procesos de control. En este contexto, algunos autores han propuesto la utilización de instrucciones verbales. Sin embargo, a diferencia de los estudios clásicos en los que se alternaba entre dos tareas únicamente, aún no existe evidencia acerca de qué zonas están involucradas en el procesamiento de la información específica de la instrucción antes de que aparezca el estímulo objetivo. Con este objetivo en mente, realizamos el Experimento II, en el cual utilizamos de nuevo resonancia magnética en conjunción con un extenso número de instrucciones verbales. Además, en este estudio sacamos partido de innovaciones en el análisis de datos de resonancia, concretamente, el análisis multivariado de patrones, para evaluar qué zonas representan diferencialmente el contenido de la instrucción durante su codificación y preparación, así como la relación de estas áreas con índices comportamentales de ejecución. De forma adicional, implementamos diversas modificaciones respecto a los paradigmas utilizados previamente para incrementar la separación de los procesos de interés (codificación, preparación e implementación de la instrucción).

DISCUSIÓN GENERAL

1. Resumen general de resultados

El trabajo de esta tesis se enmarca en la vertiente proactiva del control cognitivo, prestando especial atención a los mecanismos de preparación. En primer lugar, un objetivo de la tesis fue evaluar la relación entre estos mecanismos de control y un proceso íntimamente relacionado: la consciencia (Objetivo 1). A lo largo de una serie de experimentos comportamentales, nuestros resultados ponen de manifiesto, en línea con estudios previos, la capacidad de información subliminal de influir en la selección de un *set* de tarea por encima de otro. Sin embargo, esta influencia sólo tuvo lugar cuando el contexto era configurado adecuadamente de forma consciente. Esto es coherente con estudios y modelos previos, y supone la primera evidencia de este tipo de efecto sobre los sets *de tarea*. Adicionalmente, este trabajo revela algunas diferencias cualitativas entre el umbral objetivo y subjetivo de consciencia.

Con la intención de caracterizar la función subyacente a estos procesos de preparación, el Experimento I de la tesis tuvo como objetivo la evaluación de los índices neurales asociados a los mismos en un contexto libre de interferencia (Objetivo 3). Para ello, utilizamos *fMRI* en conjunción con una modificación del clásico paradigma empleado en este contexto. Los resultados de neuroimagen muestran que incluso bajo estas circunstancias, aquellas zonas implicadas en el procesamiento selectivo de cada una de las tareas (e.g. el giro frontal inferior izquierdo en la tarea semántica, y el lóbulo parietal superior derecho en la tarea espacial) se activan ante la presentación de las claves. En otras palabras, algunas zonas involucradas de manera específica en cada tarea son reclutadas de manera anticipatoria, antes de la aparición de la demanda. Además de las zonas involucradas específicamente en una tarea, una serie de regiones asociadas tradicionalmente al control, tales como la ínsula, y las cortezas parietal, prefrontal lateral y medial, se activan de manera inespecífica en ambas tareas. Estos resultados sugieren que la función principal de estas influencias *top-down* no respondería a un cariz exclusivamente reactivo de cara a otros sets, así como que estas no se deben a una preparación general inespecífica (Meiran, Chorev, & Sapir, 2000). Por el contrario, nuestros datos apunta a que estas influencias subyacen a mecanismos proactivos que buscan la eficiencia del comportamiento utilizando aquella información que permita generar expectativas fiables.

Pese a la relevancia de los resultados obtenidos con el paradigma anterior, estos se enmarcan en un contexto en el cual las demandas de control son relativamente bajas. En el Experimento II de la tesis, nuestro objetivo (Objetivo 4) fue estudiar los procesos asociados a la preparación en un contexto que requería la formación y activación de un nuevo set de tarea en cada ensayo. Crucialmente, a diferencia de estudios previos, nuestro paradigma nos permitió distinguir las activaciones asociadas a la codificación o implementación de las instrucciones de aquellas relacionadas directamente con el período de preparación. Adicionalmente, empleando análisis multivariados de *fMRI*, nuestros resultados revelaron que los patrones de actividad en zonas de control y de procesamiento selectivo portaban información acerca de la categoría de la instrucción, segundos antes de su implementación. Por último, descubrimos que la calidad de las representaciones en algunas de estas regiones estaba relacionada con índices comportamentales. Este patrón de resultados pone de manifiesto, en primer lugar, cierta automaticidad en el procesamiento de instrucciones verbales. Por otro lado, revela el gran impacto de influencias *top-down* en los procesos preparatorios ante situaciones novedosas y complejas. En general, nuestros datos sugieren la capacidad de los seres humanos para generar un nuevo *set* de tarea y responder, en cuestión de segundos, a estimulación compleja en base a las reglas del mismo.

A continuación, pasamos a discutir en profundidad el papel de elementos abajo-arriba (a partir de ahora, *bottom-up*) y *top-down* en los mecanismos de control proactivo. Por último, proponemos un marco teórico en el cual la interacción de ambos tipos de elementos es la que da pie a nuestra experiencia psicológica.

2. Automaticidad y control proactivo: papel de componentes *bottom-up*

En todos nuestros experimentos, como revisaremos a continuación, se pone de manifiesto la predominancia de influencias *top-down* en los procesos de preparación. Esto, sin embargo, no impide un rol potencial de elementos *bottom-up* (esto es, información entrante en el sistema) en situaciones que requieren control. La mayor evidencia en este sentido la encontramos en el Serie Experimental I. A lo largo de los diferentes experimentos comportamentales de la serie, demostramos la existencia de influencias inconscientes a la hora de seleccionar un *set* de tarea concreto. Este resultado es coherente con otros estudios que demuestran influencias inconscientes en procesos de control (van Gaal et al., 2012). En esta línea, el hecho de que el efecto de la señal en situaciones estrictas de invisibilidad sea menor que cuando esta es consciente podría ser explicado por un empobrecimiento de la señal perceptiva con la que el sistema tiene que trabajar en estos casos (Lau & Rosenthal, 2011). Esto también explicaría que el tamaño del sesgo sea similar entre situaciones conscientes y situaciones en los que el estímulo se presenta bajo el umbral subjetivo de consciencia. En cualquier caso, este sesgo inconsciente pone de manifiesto que ciertos mecanismos de control proactivo pueden verse, cuanto menos, afectados significativamente por información *bottom-up*, indistintamente de la experiencia consciente asociada a la misma. En tanto en cuanto revelan la activación de mecanismos de control de forma inconsciente, estos resultados, en conjunción con estudios previos con conclusiones similares (De Pisapia, Turatto, Lin, Jovicich, & Caramazza, 2011; Mattler, 2003; Reuss et al., 2011; Zhou & Davis, 2012), sugieren la disociación entre control y consciencia (Hommel, 2017).

Más allá de la influencia de información inconsciente en procesos de control proactivo, nuestros resultados de los Experimentos I y II también muestran cómo algunos estímulos elicitan procesos de control de forma relativamente automática. Por ejemplo, el Experimento I pone de manifiesto la capacidad de señales abstractas para reclutar zonas de control en un situación libre de interferencia, en la que por las demandas explícitas de control son menores. Por otro lado, el Experimento II sugiere la capacidad de las instrucciones verbales para reclutar zonas asociadas con control, incluso cuando los participantes no saben si van a tener que implementar estas instrucciones. Esto es coherente con resultados previos que demuestran la activación automática de ciertos componentes del *set* de tarea al codificar instrucciones, independientemente de su relevancia (Liefooghe, Wenke, & De Houwer, 2012). La habilidad de las instrucciones para elicitar ciertos componentes de control de manera automática puede subyacer a la crucial relevancia evolutiva de este tipo de aprendizaje en nuestro desarrollo como especie (Cole et al., 2013).

3. Efectos *top-down* asociados a control proactivo y sets de tarea

A pesar de la relativa automaticidad descrita en el apartado anterior, nuestros datos demuestran la abrumadora predominancia de componentes *top-down* en los procesos de control proactivo. En primer lugar, las influencias *top-down* del control proactivo son evidentes la Serie Experimental I. En este caso, pese a la existencia de un sesgo inconsciente en la selección de *sets* de tarea, los resultados sugieren un importante rol del esquema general de tarea, formado de acuerdo a metas y objetivos (Kiefer, 2007, 2012). Así, el efecto inconsciente tiene lugar solo cuando este esquema está configurado de manera adecuada. Por consiguiente, la percepción subliminal por sí misma, como estimulación *bottom-up* exclusivamente, puede afectar pero no iniciar procesos de control (van Gaal et al., 2012).

El Experimento I, por su parte, pone de manifiesto cómo las expectativas acerca de demandas futuras sesgan la actividad cerebral durante el período preparatorio. Concretamente, mientras que algunas regiones (frontoparietal e ínsula, principalmente) parecen estar involucradas en los procesos de control en sí (Dosenbach et al., 2008; Duncan, 2010), otras regiones son reclutadas de manera específica en función de la demanda esperada. Algunas de estas regiones son las mismas implicadas posteriormente en la resolución de la demanda. En el marco teórico que venimos trabajando, el cual define el control proactivo como el mantenimiento activo de información relevante en base a las metas del sujeto (Braver, 2012), podemos entender estas actividades específicas como el resultado de una influencia *top-down*, originada en las regiones de control, sobre el procesamiento de información entrante. En este sentido, nuestros resultados son difícilmente explicables por un efecto *bottom-up* de las señales, ya que estas no están asociadas en términos perceptivos a las tareas que anticipan. En otras palabras, no sería factible que el tipo de claves utilizadas *per se* activaran regiones asociadas específicamente a las tareas que señalan.

Por último, el Experimento II aporta más evidencia a favor de efectos *top-down* asociados al set de tarea. En primer lugar, aunque antes hemos mencionado cómo las instrucciones pueden involucrar a zonas de control en una manera relativamente automática, este experimento reveló cómo la preparación activa hace partícipes a zonas de control adicionales, necesarias para implementar la respuesta. De forma crucial, en este experimento demostramos cómo información específica de la instrucción es codificada en diversas zonas de control y de procesamiento selectivo durante los períodos de codificación y preparación. Esto implica de nuevo un sesgo en el procesamiento de la información en base a las metas establecidas por la instrucción. Estos patrones de actividad específicos no pueden ser explicados en ningún caso por un efecto *bottom-up* de la estimulación entrante, al consistir esta en oraciones verbales complejas (en el caso del período de codificación), o simplemente en un punto de fijación (en el caso de la preparación). Adicionalmente, el hecho de que la discriminabilidad entre categorías de instrucción en estas zonas correlacione significativamente con la ejecución pone de manifiesto el impacto de estos efectos *top-down* en nuestro comportamiento (Etzel, Cole, Zacks, Kay, & Braver, 2015).

En general, podríamos considerar que el control proactivo configura el sistema de manera *top-down* para permitir cierto grado de automaticidad de la estimulación entrante (Dehaene & Naccache, 2001; Kiefer, 2012; Kiefer & Martens, 2010). Esto, a su vez, otorgaría una mayor eficacia a nuestros sistemas de control proactivo, al reducir los costes de la monitorización mantenida en el tiempo, optimizando el proceso de consecución de metas y objetivos (Kiefer, 2012). La relación entre procesos *bottom-up* y *top-down* es discutida a continuación.

4. Control proactivo: una interacción dinámica de influencias *bottom-up* y *top-down*

Los resultados obtenidos en esta tesis ponen de manifiesto la presencia de componentes *bottom-up* y *top-down* en situaciones que elicitan control proactivo. Un aspecto importante es entender de qué manera estos componentes interactúan. En este sentido, adoptamos como marco de referencia la teoría del *predictive coding* (Friston, 2005). Esta teoría de inspiración bayesiana propone que nuestra experiencia psicológica del mundo no es el resultado de un proceso pasivo de procesamiento de la información entrante. Por el contrario, sugiere que zonas de control generarían predicciones acerca de esta información. Posteriormente, y de forma iterativa, estas predicciones afectarían de manera *top-down* el procesamiento *bottom-up*, al mismo tiempo que el componente *bottom-up* ayudaría en el moldeamiento de las predicciones de cara a próximas interacciones. Esta serie de interacciones daría lugar, en última instancia, a fenómenos como la percepción.

Un mecanismo de este tipo permitiría, a nivel evolutivo, el desarrollo de sistemas de control proactivos: a partir de la información disponible en el medio podemos generar modelos internos acerca de cómo funciona este, y, posteriormente, utilizar estos modelos para predecir cómo funcionará en el futuro (Buschman & Miller, 2014).

Por ejemplo, basándonos en reiteradas experiencias con diferentes rutas hacia nuestro lugar de trabajo, podemos predecir cuál de ellas nos será más rápida y guiar nuestra elección de acuerdo a esta predicción. El aspecto clave del control, sin embargo, es la generalización de estos modelos a situaciones nuevas con las que no tenemos experiencia previa. En nuestro ejemplo, podemos emplear el modelo generado en relación al lugar de trabajo a la hora de escoger la ruta hacia otro lugar en el que no hemos estado antes. En otros términos, el aspecto esencial del control proactivo reside en que “uno debe utilizar conocimiento previo para planificar adecuadamente las acciones y mantenerse en la tarea mientras se consigue la meta” (Buschman & Miller, 2014). Esta interiorización de experiencias basada en la interacción *bottom-up – top-down* nos permite, en definitiva, no ser meros reactores ante la estimulación entrante, sino moldear esta estimulación de acuerdo a nuestros objetivos.

5. Interrogantes y direcciones futuras

Pese a que los resultados obtenidos en esta tesis aportan evidencia relevante en el campo, algunas incógnitas permanecen sin respuesta. En cuanto a los mecanismos neurales de preparación, nuestro trabajo está basado en datos de *fMRI*. Estos datos aportan información importante a nivel espacial, es decir, acerca de qué regiones cerebrales parecen estar implicadas en estos procesos. Sin embargo, la evidencia respecto a aspectos dinámicos de la preparación, en tanto en cuanto la resolución temporal de la *fMRI* es baja, es escasa. Algunos estudios (e.g. Cole et al., 2010) han empleado magnetoencefalografía para evaluar la implementación de instrucciones verbales. Esto apunta a una gran utilidad de técnicas como esta o como la electroencefalografía para capturar la dinámica de los procesos de preparación. Por otro lado, debido a que técnicas como la *fMRI* o la MEG se basan en inferencias de los cambios en la actividad cerebral, no existen datos que demuestren de una manera causal la implicación de diferentes regiones en el procesamiento de preparación de situaciones complejas. Técnicas que interrumpe la actividad de ciertas regiones han sido utilizadas con éxito en paradigmas clásicos con este objetivo en mente (Muhle-Karbe et al., 2014). Futuros estudios quizá puedan beneficiarse de este tipo de estrategia, empleando, por ejemplo, estimulación magnética transcraneal o neurofeedback, para caracterizar el papel causal de las diferentes regiones implicadas mostradas en el Experimento II.

Por último, en esta tesis se ha evaluado la relación entre control proactivo y consciencia en situaciones repetitivas. En futuros trabajos, será interesante estudiar esta relación en situaciones altamente complejas y cambiantes, donde el requerimiento de consciencia (como integración de información) se intuye mayor. En este sentido, recientes innovaciones técnicas, como el neurofeedback multivariado, apuntan a ser de gran utilidad a la hora de diferenciar procesos difícilmente disociables hasta ahora, como por ejemplo los procesos de control que permiten una ejecución exitosa y la consciencia sobre esa ejecución (Cortese et al., 2016).

Estas innovadoras técnicas abren la puerta a nuevas investigaciones en el campo del control proactivo. Una caracterización precisa de este tipo de mecanismos no solo es importante de cara a entender el funcionamiento de nuestros sistemas cognitivos y nuestro cerebro. Crucialmente, la existencia de ciertas poblaciones en las que los mecanismos proactivos están alterados, como por ejemplo en el trastorno de déficit por hiperactividad (Grane et al., 2016), en pacientes neuropsicológicos con daño prefrontal adquirido que presenten síndromes disejecutivos (Solbakk & Løvstad, 2014), o incluso en el envejecimiento sano (Manard, François, Phillips, Salmon, & Collette, 2017), pone de manifiesto la necesidad de seguir ampliando nuestro conocimiento en este campo.

CONCLUSIONS

1. The influence of unconscious information can reach task set selection. This is true even under very restricted conditions of visibility, which argue against residual perception as an alternative explanation. When using a more ecological measure of subliminal perception, namely a subjective threshold of consciousness, the effect of subliminal cues on task selection was significantly larger. This suggests that the cause of a weaker effect of unconscious information under extremely restricted visibility might be, at least in part, due to a degradation of the perceptual signal rather than a lack of consciousness.

2. The unconscious effect under the objective threshold of consciousness was significantly modulated by conscious expectations regarding task and trial structure. In line with previous studies and theoretical models, we showed how this effect of subliminal perception took place only when congruent goals were set consciously.

3. On the contrary, conscious expectations did not have an effect on subliminal perception under the subjective threshold of consciousness. This points to the fact that subjective and objective measures of consciousness are indexing different phenomena.

4. In an interference-free context, preparatory processes recruit domain-general control brain areas together with regions of selective processing that are specifically involved in forthcoming stimulation. This is in agreement with a dual nature of preparatory processes, in which both unspecific and category-selective processes support proactive control.

5. Proactive control exerts its influence in a similar fashion when encoding and preparing to implement a complex verbal instruction. Domain-general frontal regions are involved as soon as the new task set is encoded. Crucially, parietal control regions engage only when preparation is demanded explicitly. This reveals that despite a partial automatic effect of instructions in the creation of new task sets, top-down control is required to activate the link between the task set rules and the corresponding response.

6. Specific information regarding the category (faces vs. letters) of the instruction can be decoded from different brain regions seconds before its implementation. Specifically, domain-general control areas and selective-processing regions encode this information during the preparatory interval.

7. The quality of these representations has an impact on subsequent behavior, in the sense that proactive control mechanisms use relevant information prior to the implementation of new rules in order to rapidly transform verbal instructions into coherent behavior.

ABSTRACT

To adjust our behavior based in goals is a core human ability that allows us to rapidly adapt to new demands or new environments. Cognitive control, that is, the mechanism that regulates our thought and actions upon internal representations of our goals (Norman & Shallice, 1980), is thought to underlie this ability. Due to its central role in our cognitive activity, control is involved in a plethora of phenomena, and therefore it can be analyzed from different perspectives. Specifically, this thesis takes advantage of a temporal classification: reactive versus prospective control. While reactive control refers to the immediate deployment of control upon conflict detection, prospective processes allow the anticipation and corresponding adjustment to forthcoming demands (Braver, 2012). The main aim of this thesis is to advance our knowledge about proactive control.

The Experimental Series I of the present thesis aimed at assessing the relationship between preparatory processes and consciousness. While some studies point to an unconscious bias in the selection of different action schemas (e.g. Reuss et al., 2011), other studies suggest the need for a conscious experience to effectively exert proactive control (Kiefer et al., 2012; Kiefer & Martens, 2010). To answer this question, we employed a cuing paradigm together with visibility manipulations to alter the conscious experience of cues. Results show a clear effect of subliminal cues on task setting, even when visibility of cues was extremely restricted. Crucially, this unconscious effect depended on conscious intentions, insofar a correct executive setting had to be configured consciously for these unconscious influences to take place. Last, this experimental series revealed a distinct pattern of results when using an objective threshold of consciousness compared to a subjective one, suggesting that these two measures might be indexing different phenomena (Snodgrass & Shevrin, 2006).

Another aim of this thesis was to evaluate the advantages and disadvantages of using fMRI in the quest for the neural correlates of cognitive processes. This was crucial given the predominance of fMRI evidence in this thesis. Thus, we reviewed the most relevant considerations regarding fMRI use prior to carrying out our fMRI studies.

In Experiment I of the thesis we studied the neural correlated of preparatory processes. Preparation, defined as the adjust to task rules prior to the onset of a target (Rogers & Monsell, 1995), can be elicited by showing cues that signal to-be-presented demands. At the neural level, these cues engage both control and selective processing brain regions. However, previous studies did not control for interference between tasks, which is known to confound preparatory effects. Thus, it remained unknown whether preparatory mechanisms are domain-specific or domain-general. In this experiment, we found that even in a context with low interference between tasks, preparatory cues can elicit anticipatory activations both in control and selective processing regions. More specifically, some of these selective processing regions were later on engaged by targets, revealing the proactive nature of preparatory activations.

Last, in the Experiment II of the present thesis we assessed the neural indexes of preparation in a different context. Most of preparation studies employ paradigms that capitalize on the alternation between two task sets. However, control demands are thought to be larger in novel situations (Norman & Shallice, 1980). In these contexts, a new task set has to be created from scratch rather than merely being reactivated (Cole et al., 2013). Despite a profound involvement of control in this type of situation, the correlates of preparatory mechanisms in complex, novel task sets remain unclear. In this experiment, we thus assessed the neural indexes underlying the implementation of verbal instructions, insofar they require the formation and execution of novel task sets (Hartstra et al., 2011). Our results reveal, first, an initial effect of instructions that engaged frontal regions, and, second, an involvement of frontal together with parietal areas during active preparation for implementation. Moreover, our results are the first to show how different brain regions carry information in their patterns about the category of the instruction seconds before its implementation. These regions include both control and selective category regions during the preparatory period. Crucially, the quality of these representations had a direct influence on subsequent behavior, illustrating the important role of proactive control in novel contexts.

All of our experiments highlight the predominance of top-down influences in preparatory mechanisms. However, bottom-up elements also play a role in control-demanding context. The biggest piece of evidence in this line comes from Experimental Series 1, which revealed an unconscious bias in task set selection. This result is coherent with previous studies showing unconscious influences in high-level processes (van Gaal et al., 2012). It therefore shows that at least some proactive control mechanisms can be altered by bottom-up information. Subsequently, in conjunction with previous similar studies (e.g. De Pisapia et al., 2011), they suggest the dissociation between proactive control and consciousness (Hommel, 2017). Experiments I and II also show how some stimuli, such as instructions, can elicit control processes automatically (Liefooghe, Wenke, & De Houwer, 2012). The evolutive relevance of fast learning (Cole et al., 2013) can underlie this automatic effect of instructions.

Despite the relative automaticity described before, our data show an overwhelming predominance of top-down effects in proactive control. First, in Experimental Series I, the unconscious effect is only found when the executive setting is configured properly according to conscious expectations (Kiefer, 2012). Therefore, subliminal perception can affect but not initiate control processes (van Gaal et al., 2012). Moreover, in Experiment I, conscious expectations regarding future demands were shown to modulate brain activity during preparation. In the proactive control framework (Braver, 2012), the reported category specific activations can be understood as the outcome of a top-down influence, originating in control regions, on incoming information. Last, Experiment II reveals how actively preparing to implement novel task sets involves a large set of control areas. Moreover, category specific information could be decoded from selective processing regions seconds before target onset, which shows again a bias in the processing of incoming information based on internal goals. Altogether, our results suggest that proactive cognitive control sets up our information-processing system in a top-down manner to allow some extent of automaticity (Dehaene & Naccache, 2001; Kiefer, 2012; Kiefer & Martens, 2010). This, in turn, would make our control systems more efficient by reducing costs associated to maintained monitoring, and therefore, optimizing the consecution of our goals (Kiefer, 2012).

In sum, the present thesis reveals a dynamic relationship between bottom-up and top-down processes. We interpret this relationship within the predictive coding framework (Friston, 2005), which suggests that our psychological experience is the result of an iterative interaction between bottom-up information and top-down predictions that bias this information to guide perception. Such mechanism would allow the evolutive development of a proactive control system (Buschman & Miller, 2014).

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APÉNDICES

Apéndice 1

González-García, C., Tudela, P., & Ruz, M. (2015). Unconscious biases in task choices depend on conscious expectations. *Consciousness and cognition*, 37, 44-56. https://doi.org/10.1016/j.concog.2015.08.001

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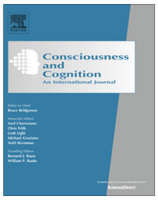

Unconscious biases in task choices depend on conscious expectations

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ABSTRACT

Recent studies highlight the influence of non-conscious information on task-set selection. However, it has not yet been tested whether this influence depends on conscious settings, as some theoretical models propose. In a series of three experiments, we explored whether non-conscious abstract cues could bias choices between a semantic and a perceptual task. In Experiment 1, we observed a non-conscious influence on task-set selection even when perceptual priming and cue-target compound confounds did not apply. Experiments 2 and 3 showed that, under restrictive conditions of visibility, cues only biased task selection when the conscious task-setting mindset led participants to search for information during the time period of the cue. However, this conscious strategy did not modulate the effect found when a subjective measure of consciousness was used. Altogether, our results show that the configuration of the conscious mindset determines the potential bias of non-conscious information on task-set selection.

1. Introduction

Several subliminal priming studies have shown that non-conscious representations have a pervasive influence on information processing (e.g. Dehaene & Changeux, 2011; Dehaene & Naccache, 2001; Kiefer, 2012; Kouider & Dehaene, 2007; Marcel, 1983; Mattler, 2003; Peirce & Jastrow, 1884; Ruz, Madrid, Lupiáñez, & Tudela, 2003; Sidis, 1898; Stroh, Shaw, & Washburn, 1908). Data from blindsight or neglect patients have provided similar results (Dehaene & Naccache, 2001; Weiskrantz, 2009). Traditionally, certain high-level processes including cognitive control were considered immune to subliminal information (Dehaene & Naccache, 2001; Hommel, 2007; Kunde, Reuss, & Kiesel, 2012; Schneider & Shiffrin, 1977; Van Gaal, de Lange, & Cohen, 2012). However, various recent studies showing that non-conscious information can influence control processes have challenged this classic idea. Some of these control processes include shifts of attention (Ansorge & Horstmann, 2007; Ansorge, Horstmann, & Scharlau, 2010, 2011), task switching (Ansorge, Kunde, & Kiefer, 2014), response inhibition, conflict monitoring, error detection (Van Gaal & Lamme, 2012), and lastly decision-making (Van Gaal et al., 2012).

Volition and cognitive control models often relate decision-making to task-set selection (i.e. 'what decisions' in Haggard's model; 2008). In the laboratory, this process has been studied using task cueing paradigms (e.g. Schlaghecken & Eimer, 2004). In the subliminal priming field, the main hypothesis is that non-conscious information modulates task selection and affects later stages of the decision process. Two initial studies explored this idea in simple perceptual choices (Kiesel et al., 2006; Schlaghecken & Eimer, 2004). In such studies, participants responded to the direction (i.e. left vs. right) of arrows

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that in some trials were preceded by additional masked arrows. Schlaghecken and Eimer (2004) found a bias to respond against the direction of the prime in long mask-target intervals, while Kiesel et al. (2006) observed a tendency to respond in the same direction as the masked arrows. Likewise, in a similar setting, Mattler (2003, 2005, 2006, 2007) showed that presenting cue-congruent masked shapes led to faster execution of the cued task. These results suggest that non-conscious information influenced participants' decisions. However, as other authors have highlighted (Reuss, Kiesel, Kunde, & Hommel, 2011), at least the results obtained by Kiesel et al. (2006) and Mattler (2003), Mattler (2006) could be explained without appealing to a non-conscious bias of decision-making. For example, perceptual priming could have enhanced target processing when it was preceded by a cue with a similar shape appearing at the same location. This explanation does not require cognitive control, as the mere presence of a cue automatically may have triggered the mobilization of attention to the target (Reuss et al., 2011). The same explanation could also be applied to similar studies (Lau & Passingham, 2007; Mattler, 2003). An alternative explanation is that of cue-target compounds. In some of those experiments (Reuss et al., 2011; Exp. 1; Schlaghecken, Klapp, & Maylor, 2009), although cues and targets differed in shape, there was a limited number of target stimuli. Thus, participants may have encoded an explicit response in their episodic memory for specific cue-target combinations (Logan & Bundesen, 2004) that may later have been triggered in a non-conscious manner without requiring any kind of cognitive control.

A recent study on task switching (Reuss et al., 2011; Exp. 2) overcame the shortcomings of explanations provided in terms of cue-target compounds by using transition cues. The design consisted of pairs of two trials: whereas participants were conscious of the first trial, which specified what they should do, the beginning of the second trial was a transition cue, indicating whether they had to repeat the previous task or switch to the other one. This design avoided cue-target compounds because cues were not linked to specific targets or responses. Crucially, transition cues were presented in a conscious or non-conscious manner. Results showed that participants performed the task instructed by the transition cue to a larger extent, even when it was non-conscious, suggesting that task sets could be non-consciously activated in situations where perceptual facilitation and cue-target compound effects were excluded. Nevertheless, in this paradigm the non-conscious cue was always preceded by a conscious task cue, which may have affected the pattern of data. In fact, a repetition effect was found, showing that participants repeated the task of (conscious) trial $n - 1$ in 65% of the trials, regardless of the task signaled by the non-conscious cue. These results suggest a significant influence of a previous conscious task set on *free* decisions. However, it is still not known whether the choice between two tasks can be non-consciously biased even without a previous conscious task cue.

1.1. Influence of conscious expectations on non-conscious information

A number of recent approaches agree on the idea of cognitive control as a set of processes that operate in a ballistic manner once they have been configured by attention and task set. Under this assumption, cognitive control must be configured properly for non-conscious automatic effects to take place. Kiefer and Martens (2010) put these ideas together in their *Attentional Sensitization Model* (later extended to different areas of unconscious cognition in Kiefer, Adams, & Zovko, 2012), according to which a given conscious task setting enhances task-relevant automatic processes but attenuates task-irrelevant ones. They considered that the conscious setting is built upon stimulus expectations and action intentions that mobilize attentional resources accordingly. Several data fit with this model (Chiu & Aron, 2014; Kiefer, 2012; Kiefer & Brendel, 2006; Kiefer & Martens, 2010; Kiefer et al., 2012; Naccache, Blandin, & Dehaene, 2002). Although the influence of conscious task setting on non-conscious biasing of task-set selection has been suggested (Schlaghecken & Eimer, 2004), this hypothesis remains untested.

1.2. Objective and subjective thresholds of consciousness

The studies reviewed so far share a common feature: the presentation time of the masked items is extremely brief. Indeed, they operate in the so-called objective threshold (OT) of consciousness, in which participants' performance is at chance levels when they discriminate between masked stimuli (Holender, 1986). This objective state of unawareness (OU) requires extremely brief stimulus presentation times and does not rely on subjective reports, so it is considered a conservative estimation of unawareness. Since it leads to more compelling positive results (Merikle, Smilek, & Eastwood, 2001), its use is preponderant in current literature (Overgaard, Timmermans, Sandberg, & Cleeremans, 2010). Thus, in our study we aimed at assessing the role of conscious expectations in objectively non-conscious biases towards task choices. We expected this to allow us to compare our results with previous ones, and to test for non-conscious effects under strict visibility conditions. Nevertheless, despite the major acceptance of objective measures, some data suggest that they underestimate the influence of non-conscious information (Merikle & Reingold, 1998) or that they explore a degraded state of non-conscious cognition (Armstrong & Dienes, 2013). Techniques based on subjective reports, on the other hand, provide an alternative or complementary approach.

The subjective threshold (ST) of consciousness assesses awareness based on participants' subjective reports. Participants who are in a subjective state of unawareness (SU) are considered to be non-conscious when they report not being able to perceive a given stimulus (Merikle et al., 2001). This way of testing consciousness fits better than other methods with the notion of consciousness of some theoretical models (Lau & Rosenthal, 2011; Rosenthal, 2008) and philosophical claims (Chalmers, 1996; Dennett, 2003, 2007). Although the usefulness of subjective indexes has been extensively discussed, their actual use has been partially neglected in the literature (see Sandberg, Timmermans, Overgaard, & Cleeremans, 2010). However, some studies conducted in the last few years have shown the unique nature of the SU as a proper non-conscious state rather than a weaker conscious phenomenon (Armstrong & Dienes, 2013; Overgaard et al., 2010; Sandberg, Bibby, Timmermans, Cleeremans, & Overgaard, 2011; Sandberg et al., 2010; Snodgrass & Shevrin, 2006). According to some authors (Snodgrass, Bernat, & Shevrin, 2004; Snodgrass & Shevrin, 2006), objective and subjective thresholds index different types of unawareness. Specifically, they consider that a stimulus under the OU is both phenomenally (that is, perceptually, in Snodgrass' framework) and reflectively unconscious. This reflective consciousness refers to a "higher-order metacognitive process involving reflecting upon and evaluating various phenomenal contents" (Snodgrass & Shevrin, 2006). By contrast, SU stimuli are considered to be phenomenally conscious but again reflectively unconscious. Crucially, the output of this configuration is a state of unawareness qualitatively different from OU but also from awareness (i.e. conscious awareness; CA). So far, the effect of a conscious setting on non-conscious processing has been studied under OU conditions. However, to the best of our knowledge, there is no previous empirical evidence regarding the influence of conscious expectations on SU stimuli. Since under SU conditions the (first-order) representation of the stimulus is relatively intact, we hypothesized its processing to be independent of (higher-order) conscious strategies, namely expectations, as it has been previously suggested: "stimuli [under SU] are typically ignored, but nonetheless exert various influences unnoticed and unmodified by reflective consciousness and its tools (i.e. higher-level response strategies)" (Snodgrass & Shevrin, 2006).

2. Experiment 1

In this first experiment, we sought to replicate previous results on non-conscious modulation of task selection using a novel paradigm. Here, single cues instructed participants to perform one of two different tasks. Whereas participants had to follow the instructions of the cues they perceived consciously, they were told that in some trials there would not be any informative cue and that in those trials they should freely choose between the two tasks. Based on previous studies (Reuss et al., 2011), we predicted that even cues presented at OU would bias participants' choices.

2.1. Method

2.1.1. Participants

Twenty-four students of the University of Granada (4 males, 4 left-handed, mean age 20.5 years) participated in the experiment in exchange for course credits. They were all Spanish native speakers, had normal or corrected-to-normal vision and signed an informed consent form approved by the local Ethics Committee.

2.1.2. Apparatus and stimuli

A total of 300 Spanish words were used as targets (all of them were nouns; mean number of letters 5.5; range 2–8; mean frequency 49, range 1–184). Half of them referred to natural elements (e.g. mountain), whereas the other half designated man-made items (e.g. chair). Half of the words in each category had one of their letters altered, that is, they were noticeably bigger or smaller than the others, while the other words were perceptually unaltered. A white triangle in two different orientations (upwards or downwards) was used as cue. Additionally, a square composed of irregular black and white bars was used as mask. All stimuli were presented in a silver-gray background. The presentation of stimuli was developed and controlled using E-Prime experimental software, 2.0.10 version (Schneider, Eschman, & Zuccolotto, 2002) and run on a 17″ LG FLATRON L1718s screen with a 60 Hz refresh rate. The room was illuminated using a single 25 W light bulb. The luminance of the room was measured using a photometer and set at 5.2 candelas per square meter (cd/m^2).

2.1.3. Procedure

Each of the 300 words could be analyzed in two dimensions, namely a semantic and a perceptual one. At the semantic level, participants had to distinguish between words referring to either natural or man-made elements; at the perceptual level they had to report whether or not the target word contained an altered letter (i.e. larger or smaller than the others). Thus, in each trial participants had to perform one of the two tasks with the same set of targets. Each target was preceded by a cue that indicated the specific task to perform. Participants responded by pressing the Z, X, N or M keys (one for each possible response) on the keyboard. The index fingers of each hand (X and N keys) were used for one task and the middle fingers of each hand (Z and M keys) were used for the other task. The assignment of the orientation of the triangle and keys to tasks and responses was fully counterbalanced. Therefore, both the hand and the finger associated to a given response changed across participants. Cues were preceded and followed by masks. The proximity between cue and masks was set at three different fixation intervals, which modulated the degree of visibility of the cue. The fixation cross was presented during these intervals to help focus the attention of participants to the cue location. These intervals were adjusted approximations to the screen refresh rate (16.73 ms). The OU, SU and conscious awareness (CA) conditions, respectively, had intervals of one (16.73 ms), three (47.1 ms) and six (100.6 ms) refresh rates between masks and cue. Additionally, the interval between the post-cue mask and the target (mask-target interval; MTI) was either short (17 ms) or long (1000 ms). This was included to explore whether having more or less time to get prepared influenced the potential non-conscious bias (Altmann, 2004; Meiran, 2000; Meiran, Chorev, & Sapir, 2000; Meiran, Hommel, Bibi, & Lev, 2002).

The main task consisted of 300 trials, presented randomly. Before the main task, participants performed a few practice trials. In every trial, after a 100 ms fixation point (0.7°), a 30 ms cue (upward or downward triangle; 4° × 4°) was preceded and followed by two masks (4° × 4°) of 200 ms of duration each. After the MTI, the target word (mean 3.8°) was presented for 200 ms. After the presentation of the target, participants responded during a 2500 ms fixation point (see Fig. 1).

Participants were asked to focus on the cues and respond in accordance with them even if they were not completely sure about which cue had appeared. Furthermore, they were told that no cues would be presented in some trials and that, in such cases, they should freely choose which task to perform. Cues were actually presented in all trials, although their visibility (and therefore, participants' awareness) varied according to the cue-mask interval.

To maintain similarity with previous studies (e.g. Reuss et al., 2011) to a maximum, thresholds of consciousness were not measured initially for each participant. Although doing so would have been desirable, estimating the thresholds in advance would have arisen suspicions in participants regarding the presence of cues in every trial. This could have undermined the instructions in the main task of choosing freely when "no cue was presented". Hence, thresholds were determined based on duration details obtained in previous studies (e.g. Reuss et al., 2011; Ruz et al., 2003) and pilot experiments performed using the current task. Such results suggested that the variability of thresholds among participants was small, so we used the values that were optimal for the OU and SU thresholds. Nonetheless, thresholds were checked individually after the main task. In the next sections, we will describe how we assessed OU and SU.

2.1.4. OU and SU measurement

In order to obtain an *objective* index of unawareness, participants had to perform forced-choice discriminations between the upward and downward triangles. One hundred and fifty trials were run with the same experimental structure of events in the main task. Participants were instructed to ignore the words and focus on the orientation of the triangle. They had to press either the Q or P keys to report whether the triangle pointed up or down (key assignments were counterbalanced across participants).

Afterwards, we queried participants about their *subjective* perception of the cue at every threshold of visibility. Although there has been a long debate about which subjective technique captures participants' experience better, empirical data support the use of graduated scales, such as the Perceptual Awareness Scale (PAS; Ramsøy & Overgaard, 2004). Specifically, the PAS has been considered "the most exhaustive" index for SU among a number of different measures (see Sandberg et al., 2010). We thus ran a short block of eighteen trials arranged as in the main task and presented a Likert-type scale that was similar to the PAS at the end of each one. Participants had to choose the number that better described their subjective cue perception on a scale ranging from 1 – labeled as "no subjective perception of the cue" – to 9 – labeled as "total awareness of the presence of the cue". These labels were used following the original PAS (Ramsøy & Overgaard, 2004). We increased the size of the scale from the original version (range 1–4) to give participants a larger number of alternatives and consequently reduce the occurrence of false negatives and positives (i.e. partially conscious states tagged as non-conscious and vice versa).

2.1.5. Design

The experiment had a within-participants design both for the main and the threshold assessment tasks. In the main task, we introduced the factors Task (perceptual vs. semantic), Visibility (OU, SU and CA), MTI (short vs. long) and Switch (same vs. different cue from the previous trial). We introduced the switch factor in accordance with previous studies (Reuss et al., 2011) that suggested the potential key role of cue repetition in this type of paradigms.

2.2. Results

Two of the participants were excluded from the analyses due to high error rates (over 30% of the trials).

2.2.1. Decision-making analysis

Following previous studies (Reuss et al., 2011; Schlaghecken & Eimer, 2004), we transformed participants' responses into an index reporting the percentage of times they had performed the cued task under each condition. Next, we introduced these data into a repeated-measures ANOVA. We applied the Greenhouse-Geisser correction to correct for sphericity violations when needed.

2.2.1.1. Cue biases at different thresholds of consciousness. The ANOVA yielded a main effect of Visibility, $F(2, 20) = 335.62$, $p < .001$, $\eta_p^2 = .97$, showing a significant increase in cue-congruent responses at SU ($M = 90.4$; $SD = 1.7$) compared to OU ($M = 51.8$; $SD = 1$), and at CA ($M = 95$; $SD = 1.1$) compared to SU. Both SU, $t(21) = 23.86$, $p < .001$, and CA scores, $t(21) = 41.34$, $p < .001$, differed from chance, whereas the OU score approached significant levels, $t(21) = 1.8$, $p < .09$. Crucially, the Switch factor modulated this main OU effect, $F(2, 20) = 3.58$, $p < .05$, $\eta_p^2 = .26$. At OU, the score was higher in cue-repetition trials ($M = 56.1$; $SD = 1.9$) than in no-repetition trials ($M = 47.4$; $SD = 1.7$), $F(1, 21) = 8.26$, $p < .01$, $\eta_p^2 = .28$. Whereas the former significantly differed from chance, $t(21) = 3.2$, $p < .005$, no differences were found in no-repetition situations, $t = -1.52$, $p = .14$.

2.2.1.2. Mask-target interval and Switch effects. The ANOVA yielded a main effect of MTI, $F(1, 21) = 7.17$, $p < .02$, $\eta_p^2 = .25$, since participants performed the cued task more often in the short ($M = 80.3$; $SD = .9$) than in the long ($M = 77.7$; $SD = 1$) MTI. There was also a main effect of Switch, $F(1, 21) = 7.22$, $p < .02$, $\eta_p^2 = .26$, as participants followed the cue to a greater extent when it was not repeated ($M = 80.9$; $SD = 1$) than when it was repeated ($M = 77.7$; $SD = 1.1$). These two factors interacted, $F(1, 21) = 6.45$, $p < .02$, $\eta_p^2 = .24$, revealing that whereas there were differences between no repetition ($M = 77$; $SD = 1.5$) and cue-repetition trials ($M = 83.6$; $SD = 1$) in the short MTI, $F(1, 21) = 13.82$, $p < .002$, $\eta_p^2 = .4$, these differences disappeared in long MTI trials, $F > 1$. However, neither the MTI × Visibility interaction, $F = 3.36$, $p > .05$, nor the MTI × Switch × Visibility interaction, $F = 1$, $p > .3$, were significant.

2.2.2. Objective index analysis

Participants' responses in the forced discrimination procedure were classified as hits, misses, false alarms and correct rejections. These data were transformed into a d' index. As expected, a single-sample t-test revealed that d' differed from zero both at CA ($M = 4.5$; $SD = .3$), $t(21) = 16.7$, $p < .001$, and at SU ($M = 4.2$; $SD = .69$), $t(21) = 28.48$, $p < .001$. By contrast, the d' at OU did not differ from zero ($M = .16$; $SD = .48$), $t(21) = 1.5$, $p > .13$, suggesting that participants' ability to detect specific OU stimuli was at chance levels.

To ascertain that the biases found in choices after non-conscious cues were not generated by changes in cue awareness, we assessed whether d' was modulated by the Switch factor, which was not the case ($F < 1$).

2.2.3. Subjective index analysis

To analyze subjective reports, we obtained an average Likert score for each threshold of consciousness and participant. A repeated measures ANOVA yielded a main effect of Visibility, $F(2, 20) = 161.62$, $p < .001$, $\eta_p^2 = .94$. The OU score ($M = 1.68$, $SD = 1.3$) differed from the SU score ($M = 6.69$, $SD = 2.15$), $F(1, 21) = 124.9$, $p < .001$, $\eta_p^2 = .86$, and from the CA score ($M = 7.9$, $SD = 1.34$), $F(1, 21) = 313.84$, $p < .001$, $\eta_p^2 = .94$. The SU score also differed from the CA score, $F(1, 21) = 20.6$, $p < .001$, $\eta_p^2 = .46$. Despite this significant difference, the SU score was higher than expected (Ramsøy & Overgaard, 2004; Sandberg et al., 2011). This issue will be discussed in the next section.

2.3. Discussion

Our results support the idea that decisions made by participants can be biased by symbolic information that is not perceived consciously. In the OU condition, participants chose to perform the task signaled by the non-conscious cue to a larger extent, but only when it matched the cue in the previous trial. Surprisingly, cues presented at SU generated similar effects to conscious ones, that is, participants followed the cue instructions in a large percentage of trials. Unfortunately, participants' subjective reports in this SU condition were unexpectedly high. Although they were statistically different from reports for cues presented consciously, such high scores limit the scope of the inferences that can be made regarding SU results. Hence, in the following studies of this series we reduced the cue-mask intervals to obtain a more accurate SU.

Overall, results from Experiment 1 provide suggestive evidence of non-conscious activation of task sets, in agreement with previous studies (Kiesel et al., 2006; Reuss et al., 2011; Schlaghecken & Eimer, 2004; Weibel, Giersch, Dehaene, & Huron, 2013). However, an alternative explanation could be that participants in OU trials displayed a tendency to repeat the previous decision, which may have led to the effects that we observed only in non-switch trials. To obtain evidence against this explanation and to explore the dependence of the effect on the conscious mental state, we performed Experiment 2. As mentioned in the introduction, recent theoretical and experimental approaches in the field propose that non-conscious biases depend on conscious intentions and expectations (Kiefer & Martens, 2010; Kunde, Kiesel, & Hoffmann, 2003; Naccache et al., 2002; Schlaghecken & Eimer, 2004), although it is not yet known whether these influences apply to free decisions. In Experiment 2, we presented cues of different visibility in separate blocks and thus manipulated participants' expectations by making cue visibility predictable. Hence, participants knew in advance whether they would perceive the cue in the next trial. As in Experiment 1, participants were instructed to freely choose the task to perform when "no cue was present" (i.e. non-conscious cued trials). In line with current theories (Kiefer & Martens, 2010), we hypothesized that the prediction of an incoming non-conscious trial would eliminate the non-conscious influence of cues as participants would no longer seek for this information in blocks in which they expected that no cue would be presented. By contrast, if the bias observed in Experiment 1 was the result of a tendency to repeat the previous decision and unrelated to non-conscious processing, we should obtain the same effect in Experiment 2.

3. Experiment 2

3.1. Method

3.1.1. Participants

Twenty-four students of the University of Granada (1 men, 2 left-handed, mean age 22 years) participated in the experiment in exchange for course credits. They all were Spanish native speakers, had normal or corrected-to-normal vision, and signed an informed consent form approved by the local Ethics Committee.

3.1.2. Apparatus and stimuli

The same stimuli as in Experiment 1 were used. The experiment was conducted using the same version of E-Prime, running on the same computers and under the same lighting conditions.

3.1.3. Procedure

The experiment structure was very similar to Experiment 1, with the major difference that we presented trials of different visibility in blocks rather than in random order. The sequence of blocks was counterbalanced across participants. As in Experiment 1, participants performed a few practice trials after the instructions. During these practice trials, they learned to choose between the two tasks when they had no awareness of the presence of the cue (OU and SU blocks). Additionally, based on the results from Experiment 1, we reduced the cue-mask intervals in the SU condition from 3 to 2 refresh rates (33.46 ms) to obtain a more accurate SU. The use of blocks and the new SU interval were also applied to the threshold-checking procedures. The remaining details did not change from Experiment 1.

3.2. Results

One participant was excluded from the analyses due to an excessive error rate (over 30% of the trials).

3.2.1. Decision-making analysis

3.2.1.1. Cue biases at different thresholds of consciousness. We found an effect of Visibility, $F(2, 21) = 160.7$, $p < .001$, $\eta_p^2 = .94$. As expected, the percentage of trials in which participants followed the cue was larger at CA ($M = 95$; $SD = 1.3$) than at SU ($M = 62$; $SD = 3.7$), and was higher at SU than at OU ($M = 52$; $SD = 2$). The first two scores significantly differed from chance, $t(22) = 33.85$, $p < .001$, and $t(22) = 3.23$, $p < .005$, at CA and SU, respectively. However, the OU score was not different from chance, $t < 1$. Unlike the results of Experiment 1, these scores were not modulated by the Switch factor, $F(1, 22) = 1.26$, $p > .3$ (see Fig. 2). Additionally, we performed a new ANOVA to check whether the order of presentation of blocks affected these results. The main effect of block and its interaction with the Visibility factor were not significant (all Fs < 1).

3.2.1.2. Switch effects. The ANOVA also revealed a main effect of Switch, $F(1, 22) = 6.28$, $p < .03$, $\eta_p^2 = .22$, since participants performed the cued task more in non-switch ($M = 70.3$; $SD = 1.7$) than in switch trials ($M = 68.6$; $SD = 1.7$). An additional ANOVA ruled out an interaction between Switch and block order ($F < 1$).

3.2.2. Objective index analysis

The analysis of objective scores showed that the d' was significantly different from 0 in both the SU ($M = 2.2$; $SD = 1.7$), $t(22) = 50.1$, $p < .001$, and the CA ($M = 4.5$; $SD = .4$) conditions, $t(22) = 16.3$, $p < .001$, but not in the OU condition ($M = .3$; $SD = .9$), $t(22) = 1.7$, $p > .05$.

3.2.3. Subjective index analysis

We found a main effect of Visibility in the Likert scores, $F(2, 21) = 180.1$, $p < .001$, $\eta_p^2 = .95$. OU scores ($M = 2.2$; $SD = .3$) differed from SU scores ($M = 3.8$; $SD = .4$), $F(1, 22) = 31.18$, $p < .001$, $\eta_p^2 = .59$, and CA scores ($M = 8.3$; $SD = .2$), $F(1, 22) = 365.53$, $p < .001$, $\eta_p^2 = .94$. Again, SU scores also differed from CA scores, $F(1, 22) = 129.38$, $p < .001$, $\eta_p^2 = .86$. In contrast with Experiment 1, the SU score (3.8 out of 9) resembled the scores related to the experience of a "brief glimpse" (2 out of 4) obtained in the Perceptual Awareness Scale (Ramsøy & Overgaard, 2004; Sandberg et al., 2011). According to Ramsøy and Overgaard (2004), this score reflects "the feeling that something has been shown [...], not characterized by any content"; a feeling that "cannot be specified any further".

3.3. Discussion

As predicted, when participants believed there was no information to be searched regarding what to do next, the effect of non-conscious information presented at OU disappeared. To put it another way, our results suggest that conscious expectations about the presence of useful information for task guidance funnel the effect of non-conscious information. In addition, the current results provide support against an explanation of the non-conscious bias observed in Experiment 1 in terms of a tendency to repeat the choice made in the previous trial. The tendency to perform the cued task more frequently in non-switch than in switch trials was present in the current experiment, as evidenced by the significant main effect of Switch on decisions. Arguably, if such strategy drove the effects observed in Experiment 1, the allegedly non-conscious bias should also be present in the current experiment. This, however, was not the case.

An alternative explanation could be that cue instructions and not choice/response repetition may have generated the OU bias in non-switch trials observed in Experiment 1. In fact, the effect could be explained by a mere repetition of previously seen instructions. Since in Experiment 2 the cue was invisible throughout the whole OU block, participants were not able to repeat the instruction and consequently the effect vanished. To rule out this possibility, we performed an additional analysis of Experiment 1 including visibility in the previous trial (CA, SU, OU) as an additional factor. Results showed that this factor did not modulate the effect of the cue in the OU condition in Experiment 1, ($F = 1.1$, $p = .35$), which indicates that instruction repetition did not account for the effects we found in Experiment 1 or 2.

In addition, the SU estimation was more accurate in Experiment 2, as subjective reports were now consistent with the lack of subjective perception of the cues. In fact, the score obtained has been previously related to a low subjective experience of form (Ramsøy & Overgaard, 2004) but a high detection accuracy (Sandberg et al., 2011) in equivalent scores on the Perceptual Awareness Scale. Interestingly, the effect of SU cues was still highly significant. One could say these results are due to some degree of residual consciousness that escapes subjective reports (Block, 2007), but it is also possible that the lower degree of perceptual degradation of cues at SU helps boost their non-conscious effect in the system (Merikle et al., 2001; Snodgrass & Shevrin, 2006). We will return to this issue in the General Discussion.

Still, there was an additional alternative explanation to our results. The difference between Experiments 1 and 2 could be due to the use of an intermixed vs. blocked order rather than to the predictability of the sequence. Thus, the effect may have disappeared as a mere consequence of blocking the non-conscious trials in Experiment 2. To rule out this alternative explanation, we performed a new experiment in which we compared a random sequence with a predictable sequence of intermixed OU, SU and CA trials. By allowing this prediction to take place, we expected to eliminate the bias in OU trials again. It should be noted that this trial-by-trial sequence is stricter than a blocked one, since in the former the strategy of whether or not paying attention to the cue period has to be applied in each trial. Conversely, in a blocked setting such as that of Experiment 2, the strategy can be applied during the whole block period. Thus, Experiment 3 had two major goals: using alternating trials both in the predictable and unpredictable conditions, and replicating the results of Experiment 1 and 2 with a new sample of participants.

4. Experiment 3

4.1. Method

4.1.1. Participants

Forty-eight students (24 in each group, equivalent to the previous two experiments) of the University of Granada (7 males, 4 left-handed, mean age 20.3 years) participated in the study after signing an informed consent form approved by the local Ethics Committee and received course credits in exchange. They all were Spanish native speakers and had normal or corrected-to-normal vision.

4.1.2. Apparatus and stimuli

We used the same apparatus and stimuli as in Experiments 1 and 2.

4.1.3. Procedure

We introduced a between-participants manipulation of the predictability of the sequence of trials. Half of the participants performed a replication of Experiment 1 (with an adjusted SU as described in Experiment 2) in which the appearance of cues at different thresholds was randomized; the other half performed the task in a predictable sequence of cue visibility, which was set in advance. Trials with different thresholds of consciousness followed each other in a repetitive fashion (i.e. SU–OU–CA or OU–SU–CA; the two different sequences were counterbalanced across participants). All the within-participants factors remained the same as in previous experiments. These manipulations were used in the threshold-checking procedures as well.

4.2. Results

Three participants were excluded from the analyses due to an excessive error rate (over 30% of trials).

4.2.1. Decision-making analysis

4.2.1.1. Cue biases at different thresholds of consciousness. The analysis revealed a main effect of Visibility, $F(2, 42) = 227.26$, $p < .001$, $\eta_p^2 = .92$. As in Experiments 1 and 2, the effect of the cue increased along with its visibility (OU, $M = 52.9$, $SD = 1.1$; SU, $M = 67.8$, $SD = 2.6$; CA, $M = 93$, $SD = 1.5$). The three scores were significantly different from chance, $t(46) = 2.72$, $p < .01$, $t(46) = 7.62$, $p < .001$, and $t(46) = 30.94$, $p < .001$, in the OU, SU and CA conditions, respectively.

Importantly, OU scores differed between groups, $F(1, 43) = 5.08$, $p < .03$, $\eta_p^2 = .11$. While the OU score in the predictable group ($M = 50.3$; $SD = 5.3$) was equal to chance, $t < 1$, it was significant higher than chance in the random group ($M = 55.5$; $SD = 9.3$), $t(22) = 2.81$, $p < .015$. No differences were found between switch and non-switch trials in OU trials in either the predictable, $F < 1$, or the random group, $F = 1.80$, $p = .19$ (see Fig. 3). Along with the results from Experiment 2, this argues against a conscious repetition strategy as the explanation for the OU biases we found.

In SU trials, the Group factor modulated the switch effect, since switch ($M = 63.2$; $SD = 3.7$) and non-switch ($M = 68.2$; $SD = 3.9$) scores were different in the Predictable sequence group, $F(1, 43) = 6.01$, $p < .02$, $\eta_p^2 = .12$, but statistically equal in the Random sequence group, $F = 1.45$, $p = .24$. However, participants' decisions differed from chance level in all cases, namely switch trials, $t(21) = 3.\ 33$, $p < .004$, and non-switch trials, $t(21) = 4.95$, $p < .001$, in the Predictable sequence group, and switch trials, $t(22) = 6.2$, $p < .001$, and non-switch trials, $t(22) = 4.7$, $p < .001$, in the Random sequence group.

4.2.1.2. Mask-target interval and Switch effects. The ANOVA also yielded a Switch × MTI interaction, $F(1, 43) = 6.02$, $p < .02$, $\eta_p^2 = .12$. As in Experiment 1, the difference between switch ($M = 68.8$; $SD = 1.5$) and non-switch trials ($M = 73.2$; $SD = 1.5$) was only found in Short MTI trials, $F(1, 43) = 7.6$, $p < .002$, $\eta_p^2 = .15$. No differences were found in Long MTI situations, $F < 1$. Neither the MTI × Visibility interaction, $F < 1$, nor the Switch × MTI × Visibility interaction, $F = 1.91$, $p = .14$, were significant, suggesting that the effect of the cue in subliminal thresholds did not change across different MTI or switch situations.

4.2.2. Objective index analysis

Regarding the objective index, d' scores differed from zero both at SU ($M = 2.01$; $SD = 1.52$), $t(44) = 8.84$, $p < .001$, and CA ($M = 4.33$; $SD = .90$), $t(44) = 32.33$, $p < .001$. As expected, they did not differ from zero at OU ($M = .17$; $SD = .1$), $t = 1.84$, $p > .26$. Crucially, these results were not mediated by the Switch or the Group factors, all Fs < 1.

4.2.3. Subjective index analysis

There was a main effect of Visibility as measured by the Likert scale, $F(2, 45) = 514.12$, $p < .001$, $\eta_p^2 = .96$. Likert scores at OU ($M = 2.07$; $SD = .18$) were lower than at SU ($M = 4.36$; $SD = .36$) and at CA ($M = 8.6$; $SD = .13$). Neither the main effect of Group nor its interaction with the Visibility of the cue were significant, all Fs < 1. SU scores matched those obtained with the Perceptual Awareness Scale using similar time intervals (Ramsøy & Overgaard, 2004; Sandberg et al., 2011).

4.3. Discussion

The expectations about the presence or not of information useful to guide our behavior are a crucial modulator of the bias that non-conscious information exerts in simple dichotomous decisions. Our results show that cues presented at OU biased participants' choices, but only when the unpredictability of the sequence set them to search for cue information in every trial. By contrast, when the sequence of events led them not to expect cues in certain trials, their effect at OU vanished. This suggests that non-conscious OU bias in decision-making is a true phenomenon but that it depends on an appropriate conscious mindset to take place (Kiefer & Martens, 2010).

Additionally, although the cue effect was larger in short MTI trials, it did not significantly change in long MTI ones, where no differences were found between switch and non-switch trials. Since under this MTI the preparation for switch and non-switch trials is thought to be mainly equated (Altmann, 2004; Meiran, 2000; Meiran et al., 2000, 2002), the reduction of switching costs alone cannot explain the increase of a non-conscious priming effect in cue repetition trials. Instead, other processes such as accumulation of information (De Lange, van Gaal, Lamme, & Dehaene, 2011; Van Gaal, Lamme, & Ridderinkhof, 2010) may also play a role in the benefits of non-switching trials. These benefits may partially account for the non-conscious bias we found in OU conditions, rather than a simple conscious strategy to repeat the $n - 1$ task.

Moreover, the non-conscious cues presented in the SU generated a significant bias that did not interact with the predictability of the sequence as it took place in both groups to the same extent. Thus, unlike OU results, SU effects were not sensitive to the manipulation of conscious expectations. This is in line with the existence of differences in behavioral outcomes of information presented at both thresholds of consciousness (Merikle et al., 2001; Snodgrass & Shevrin, 2006), which we will discuss in the next section.

5. General discussion

The aim of the present study was to assess the influence of non-conscious information on decision making as well as the extent to which the conscious mindset modulates this influence. Results from Experiment 1 suggest that task sets can be activated outside awareness to modulate subsequent choices. Experiments 2 and 3 demonstrate that OU subliminal biases in decision making depend on conscious expectations and that the results of the previous experiment could not be fully accounted by a tendency to repeat either the previous response or the previous instruction. Additionally, we provide suggestive evidence that different states of unawareness lead to different outcomes, a result that should be taken into account in future studies.

Our data show that task-set selection is not immune to the influence of non-conscious information. Our design presented cues at different levels of visibility and random order and demonstrated that non-conscious cues can prime choices without the need of previous conscious instructions. Decision-making data, which were replicated in two separate experiments (1 and 3), point in this direction. Importantly, these results took place under very strict conditions of visibility, since d' was equal to zero, and this index was never modulated by the factors that had an impact on the non-conscious bias in the OU condition, such as sequential effects in Experiment 1 and the predictability of the sequence of trials in Experiment 3. This set of findings suggests that residual visibility was not an explanation of the biasing effects found in choices.

Another relevant and novel manipulation was the use of short and long preparation intervals (MTI). Our results showed a non-conscious bias effect when the time between the mask and the target was short, suggesting the automatic nature of the processes elicited by our paradigm. However, the effect of the cue in objective unawareness states was not significantly modulated by the MTI factor, indicating that the non-conscious bias also took place even when more controlled processing was applied.

As mentioned earlier, an initial alternative explanation could have been that participants were aware of the task they had just performed and subsequently tended to repeat it in the following trial. In Experiment 1, for instance, the cue effect in OU trials only took place in the cue repetition condition. However, even though this meta-awareness may have played a role, it cannot account on its own for the set of observed effects. First, the non-conscious bias disappeared when participants did not expect the appearance of relevant cue information, even when a general tendency to repeat the previous response was present (as evidenced by a main effect of Switch on decisions in both Experiments 2 and 3). In addition, data from Experiment 3 revealed an OU non-conscious effect also in switch trials, supporting the idea that a conscious strategy to repeat the $n-1$ decision cannot account for the non-conscious results. Awareness state measurements obtained in the three experiments point in the same direction, as the d' index was never affected by the switch factor. If participants had the tendency to repeat the previous decisions when they did not see the cue, this should have also been observed during awareness estimation, which was not the case. Additionally, one may think that this conscious strategy should have also affected SU trials, since participants were subjectively unaware of the cue as well. However, although the cue effect was greater in cue-repetition SU trials, it was higher than chance level in all cases. Altogether, these facts provide compelling evidence that conscious task repetition is not the main explanation for our results. Moreover, additional analyses suggest that a strategy to merely repeat an instruction that has been previously seen does not stand either. Nevertheless, our study was not primarily focused on the cue repetition effect so the specific role that it plays on the unconscious selection of task sets should be explored in future studies with optimized designs aimed at measuring this.

Experiments 2 and 3 showed that the OU non-conscious effects were highly dependent on conscious expectations. In Experiment 2, the predictability of cue visibility granted by blocking trials eliminated the priming effect. In non-conscious OU blocks, participants were not biased by the cue because they did not expect any useful information to be presented during the cue period. This is likely to have driven participants to stop searching for information during the cue period. In the same vein, Experiment 3 showed that this effect did not depend on the block manipulation, as it also appeared when non-conscious trials were mixed with conscious ones in a predictable sequence.

Our results are consistent with several current models of automaticity that argue that top-down conscious processes funnel non-conscious cognition and crucially extend this approach to the decision-making field in a novel way. The fundamental premise of these models is that non-conscious effects occur insofar congruent goals are set in a conscious background (Kiefer & Martens, 2010). Thus, top-down mechanisms enhance task-relevant processes while attenuating task-irrelevant information. In consequence, subliminal information is ineffective without the appropriate conscious preparation (Dehaene & Naccache, 2001). Although this prediction has been confirmed with various processes, our data are the first to provide a reliable extension of this prediction to decision-making situations (Kiefer et al., 2012). In addition, our results are also consistent with models that propose a hierarchy of control processes (Koechlin, Ody, & Kouneiher, 2003). Koechlin et al. (2003) established three levels: a first, lower level is based on premotor representations of sensory control, in which motor actions are linked to specific responses to stimuli. A second, intermediate level selects representations of the first level, based on demands of the context (i.e. task sets containing stimulus–response associations). Finally, a higher episodic control selects these contextual task sets "according to ongoing internal goals". We propose that non-conscious information exerts its influence on decision-making at the intermediate contextual level, boosting the activation of specific task sets. However, this non-conscious influence relies on higher episodic control processes, which are based on conscious expectations. In further studies, it would be crucial to test if non-conscious information can also affect these higher episodic control processes in decision-making (Newell & Shanks, 2014).

Another important finding is that the manipulation of expectations did not have an effect under SU. Moreover, the non-conscious bias was much stronger at the SU threshold than at the OU threshold. These two facts suggest that both thresholds are "indexing different phenomena" (Snodgrass & Shevrin, 2006). A conservative interpretation of this difference would claim that SU is essentially conscious, since subjective reports could be misleading (Block, 2007; Hannula, Simons, & Cohen, 2005; Holender & Duscherer, 2004). Thus, results in the SU condition are likely to be the consequence of a weaker conscious perception of which participants are not fully aware. However, an alternative explanation could be that information presented in OU conditions is extremely degraded (e.g. Lau & Rosenthal, 2011). The small effects found in this state may be due to perceptual representations of stimuli that greatly differ from normal perceptual representations. Subsequently, it would not be fair to compare OU with CA since their perceptual features are not fully equated (Merikle et al., 2001). In fact, SU effects may reflect a more accurate perceptual representation of stimuli, which would boost the non-conscious effect. The differentiation between phenomenal and reflective representations may help to shed some light on this issue. As it has been proposed previously (Snodgrass & Shevrin, 2006; Snodgrass et al., 2004), under OU conditions, both (phenomenal and reflective) representations of the stimulus are unconscious. In SU stimuli, by contrast, the phenomenal representation is likely to be conscious but the higher-order reflective process about this percept is likely to remain unconscious. This framework would explain the existence of the large cue effect in SU conditions (strong phenomenal representation) in the absence of subjective experience (in accordance with previous subjective scales results). Thus, it seems that these higher-level strategies (i.e. expectations) have a remarkable effect on OU trials but are apparently ineffective in reflective representations (SU trials). Again, this intact phenomenal representation would explain the lack of modulation of the SU effect in our experiments.

In sum, our results suggest that an adequate deployment of attentional resources is essential when the phenomenal features of stimuli are degraded to a poor representation (i.e. OU). In fact, it is widely assumed that under these circumstances, some non-conscious effects do not occur without attention (Dehaene, Changeux, Naccache, Sackur, & Sergent, 2006; Koch &

Tsuchiya, 2007). However, it has been reported that in less restrictive situations, priming effects of cognitive control processes can take place without attention (Rahnev, Huang, & Lau, 2012). This is consistent with some computational models that propose two differentiated forms of top-down attention, one for phenomenal representations and another one for higher-order reflective percepts (Raffone & Pantani, 2010). Likewise, in SU trials, the phenomenal representation of stimuli appears to be good enough not to depend on an adequate mobilization of phenomenal top-down attention. Hence, the influence of conscious expectations is likely to be weaker. Our results point to the existence of interesting evidence of subjectively unawareness states, which are currently being partially neglected in non-conscious priming literature. Future studies should take into account both subjective and objective thresholds of consciousness and assess whether this pattern of results is replicable in well-established classic paradigms.

6. Conclusions

Our study reveals several aspects of non-conscious decision-making. First, non-conscious information is able to bias a simple task choice. This bias takes place even under very restrictive conditions of visibility. Different confounds were ruled out, suggesting the non-conscious nature of the effect. Second, the bias is larger in a subjective unawareness state, probably due to a better phenomenal representation of the cue stimuli. This result endorses the use of less restrictive measures of awareness than those used to establish objective thresholds. Additionally, our results show that these two states are qualitatively different, since conscious expectations have a different weight in each condition. Whereas ongoing goals did not modulate the effect of non-conscious information at SU, they clearly had an effect at OU. Indeed, we found that goals only had an influence on task selection when they were adjusted to the features of non-conscious stimuli. This evidence altogether argues against the classical interpretation of task-set selection processes in which the given outputs of the process depend only on conscious features. Instead, our results show that the influence of non-conscious information on our choices and the different conditions that enable this should be taken into account in future studies on the field.

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Appendix A

See Fig. 1.

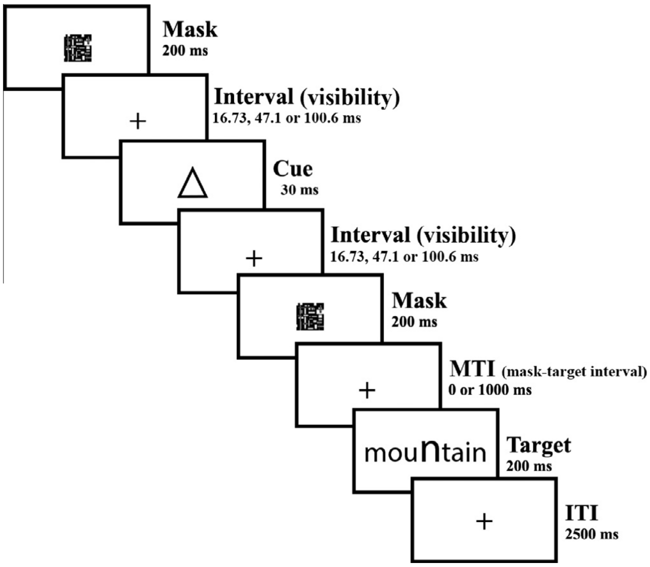

Fig. 1. Experimental procedure in phases 1 and 2 across the three experiments. Mask-cue intervals for the OU, SU and CA conditions were equivalent to 1, 3 and 6 screen refresh rates (16.73, 47.1 and 100.6 ms, respectively).

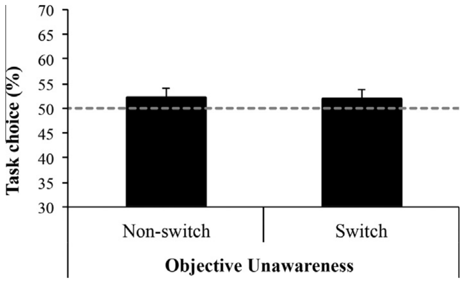

Fig. 2. Percentage of congruent responses at OU for both cue-repetition and no-repetition trials (± S.E.M.) in Experiment 2. The dashed line represents chance levels (50%).

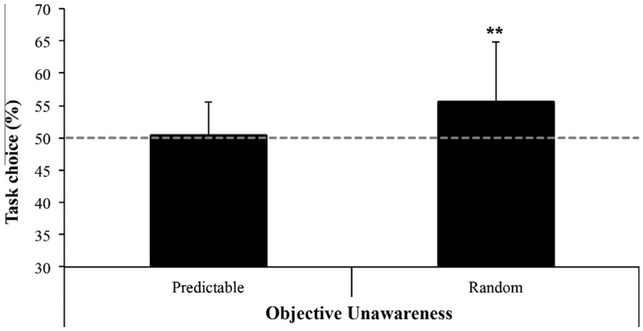

Fig. 3. Percentage of congruent responses at OU in both groups of participants (± S.E.M.) in Experiment 3.The dashed line represents chance level (50%). Stars represent statistical differences from chance ($p < .015$).

Appendix B

See Fig. 2.

Appendix C

See Fig. 3.

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Apéndice 2

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Resonancia magnética funcional: análisis crítico de sus implicaciones técnicas, estadísticas y teóricas en neurociencia humana

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Introducción. La utilización de la resonancia magnética funcional (RMf) ha supuesto una gran revolución en el avance de las neurociencias. Pese a ello, ha sido objeto de numerosas críticas.

Objetivo. Estudiar las críticas más generalizadas hacia la RMf, de manera que investigadores que se inicien en su uso conozcan los diferentes elementos que hay que tener en cuenta para un acercamiento adecuado a esta técnica.

Desarrollo. Su gran atractivo y utilidad a la hora de observar la actividad cerebral han hecho de la RMf una técnica cuyo uso ha crecido exponencialmente desde la última década del siglo XX. Paralelamente, la crítica hacia ella ha sido especialmente feroz. La mayoría de este escepticismo puede clasificarse en aspectos concernientes a la técnica y fisiología, el análisis de los datos y su interpretación teórica. Mediante este trabajo se revisarán los principales argumentos en cada uno de estos tres apartados, así como su adecuación. Adicionalmente, se pretende que este trabajo pueda servir de referencia para investigadores noveles a la hora de identificar elementos que se deban tener en cuenta en su acercamiento a la RMf.

Conclusión. Pese a que la RMf constituye actualmente una de las opciones más interesantes para observar el cerebro, es necesario un alto grado de control y conocimiento para su utilización. Aun así, gran parte de las críticas no se sostiene hoy en día.

Palabras clave. Cognición. Comportamiento. Neurociencia. Neurociencia cognitiva. Neuroimagen. Resonancia magnética funcional.

Introducción y objetivo

El estudio e interés por el cerebro ni mucho menos se ciñe a la actualidad [1]. No obstante, la aparición en la segunda mitad del siglo XX de la resonancia magnética funcional (RMf) es, sin lugar a dudas, uno de los hitos en la historia de la ciencia. Gracias a ella se consigue algo que hasta ese momento era inimaginable: poder observar qué esta 'pasando' en el cerebro de las personas cuando realizan tareas cognitivas de diversa naturaleza [2].

El principio básico en el que se basa la RMf es que, cuando una neurona trabaja, desencadena la conversión de la oxihemoglobina en desoxihemoglobina. Esta última tiene fuertes propiedades paramagnéticas, que van a desestabilizar el campo creado por el escáner de resonancia. Todo ello va a permitir cuantificar la cantidad de desoxihemoglobina en sangre, lo que, a su vez, depende de la proporción entre el oxígeno consumido y el que llega a una zona cerebral, obteniendo lo que se conoce como señal BOLD (*blood oxygen-level-dependent contrast*) [2-4]. Como veremos más adelante, la equivalencia entre BOLD y actividad neuronal ha sido uno de los puntos que más debate ha generado en torno a la RMf [3,4]. Por otro lado, debido a las características de la señal y de la técnica en sí, una vez registrada la BOLD es preciso realizar un procedimiento de preprocesamiento de la señal. Este procedimiento permitirá, en gran medida, eliminar el ruido registrado no correspondiente a la manipulación experimental. Una vez que se ha preprocesado la señal, se solapa la actividad funcional con imágenes estructurales de mayor resolución anatómica, lo cual permite localizar anatómicamente, de manera más eficaz, las activaciones. Antes de esto, cada cerebro individual se transforma en un modelo estándar mediante procedimientos matemáticos de normalización, permitiendo un mejor promedio entre los diferentes sujetos [1]. En el ámbito de la RMf, se entiende que, si comparamos la activación de los diferentes vóxeles (unidades volumétricas, análogas 3D de los píxeles) cuando el participante está haciendo una tarea determinada con la activación cuando no está llevando a cabo ninguna tarea u otra tarea distinta, el producto de la sustracción de ambas informará sobre las regiones cerebrales implicadas en la tarea [2].

Pese a la masiva aceptación de esta lógica de estudio, el papel preponderante de la RMf en la investigación actual en el campo de la neurociencia humana ha sido fuertemente atacado. Mediante esta revisión se pretende evaluar la adecuación de las principales críticas, clasificándolas en un apartado técnico-metodológico, otro estadístico y un último teórico-conceptual. El objetivo reside en poner en perspectiva estas críticas y, al mismo tiempo, evidenciar los diferentes aspectos que se deben tener en cuenta a la hora de obtener e interpretar los datos.

Aspectos técnicos y metodológicos: ¿qué mide realmente la RMf?

Cuando hablamos de asuntos técnicos, la cuestión principal consiste en definir satisfactoriamente qué mide realmente la RMf. Pese a que la lógica de actividad hemodinámica resulta bastante intuitiva, un análisis más pausado revela ciertas deficiencias. La asunción de la señal BOLD como indicador directo e inequívoco de actividad cerebral es, quizá, demasiado atrevida, si se tiene en cuenta la compleja relación entre los sistemas neuronales y los vasculares [3]. Valga de ejemplo que tanto los primeros cambios en la señal BOLD como su pico aparecen como mínimo 1 y 5 s respectivamente después de la actividad neuronal que, en principio, la provoca [1]. En este sentido, podemos enumerar una serie de factores bastante habituales que, al implicar al aparato vascular, podrían estar alterando habitualmente los datos de RMf: la mera respiración del participante, diferentes sustancias y drogas, fatiga, desinterés o cualquier otro elemento a lo largo de las diferentes condiciones experimentales afectará de alguna manera a la señal BOLD [3]. Por ello, es aconsejable que varios controles experimentales formen parte de los diseños de los estudios con el objetivo de evitar que estos efectos incidan en los datos de forma diferencial.

En cualquier caso, lo que varios autores han coincidido en señalar como la mayor fuente de problemas de interpretación de la señal a nivel técnico es precisamente la naturaleza de ésta. Pese a que todavía no disponemos de una teoría clarificadora sobre la relación real y concreta entre la actividad cerebral, el metabolismo neural y los diferentes aspectos vasculares implicados [4], lo que parece apuntarse desde diferentes estudios es la concepción de la señal BOLD como índice de actividad neural masiva supuestamente correlacionada con la respuesta vascular hemodinámica [3-5].

Propiedades de la señal BOLD: mecanismos neurofisiológicos

Una evidencia clave a favor de la lógica clásica es que, cuando se registra la actividad de las neuronas mediante electrodos, su patrón de activación suele correlacionar con los datos de neuroimagen. En concreto, diferentes experimentos con monos *Macaca mulatta* pusieron de manifiesto la alta correlación entre la señal BOLD con un índice de actividad neuronal obtenido a través de potenciales de campo local (LFP, por su siglas en inglés). Esta correlación se debe a que tanto la señal BOLD como los LFP estarían reflejando el procesamiento por parte de un grupo de neuronas del *input* de la información [5], más que su *output,* el cual quedaría reflejado en otros índices de actividad eléctrica en forma de *spikes,* como los registros uni y multicelulares, que estarían, por tanto, menos relacionados con la BOLD [6]. Tener en mente qué tipo de actividad neuronal estamos registrando no sólo será útil para comprender la señal BOLD, sino también para interpretar de manera más adecuada nuestros datos de resonancia.

Paradójicamente, a través de estas estrategias también se han obtenido datos que indican que la RMf podría estar incurriendo en un sesgo de selección de neuronas activadas [5], al no ser sensible a fenómenos de sobra demostrados, como el de las 'neuronas silenciosas', que poseen una tasa de disparo casi nula y sólo ante estímulos específicos, pero que inequívocamente deben sostener alguna función representacional, a pesar de que los experimentos de neuroimagen actuales no consigan detectarla [7]. Por otro lado, también se ha sugerido la insensibilidad de la RMf a las diferencias en el tratamiento del oxígeno de las diferentes capas cerebrales [8]. En este sentido, varios trabajos apuntan a que, en situaciones en las que clásicamente se ha asociado un descenso en la actividad neural a un descenso en el consumo de oxígeno, como, por ejemplo, cuando aparece la señal BOLD negativa [9,10], en algunas capas estaría aumentado el volumen sanguíneo [8]. Por tanto, aunque la insensibilidad de la RMf a las diferencias laminares y a las 'neuronas silenciosas' pueda no ser determinante en líneas generales, este tipo de evidencia nos debe hacer conscientes de la necesidad de cautela a la hora de interpretar nuestros datos.

Significado de los mapas de activación

Una asunción común del paradigma neurocientífico es que la activación de un área es reflejo inequívoco de su implicación en la tarea en cuestión. Autores como Logothetis [5] plantean hasta qué punto este esquema tradicional *input*-elaboración-*output* cortical no es una simplificación excesiva de la manera en la que funciona el cerebro.

Desde el punto de vista clásico, se asume una lógica lineal de funcionamiento, en la cual se presenta determinada información (*input*), un área o áreas que se activan (elaboración) y, consecuentemente, se atribuye la respuesta observable (*output*) al procesamiento en esas zonas. A través de diferentes estudios, el autor sugiere que los bucles de conexiones *feedback* y *feedforward* entre zonas subcorticales y la corteza asumidos por el esquema tradicional no serían del todo explicativos, sino que lo que debe centrar el interés son los esquemas de redes de excitación-inhibición (EIN, por sus siglas en inglés). A través de modelos computacionales, se ha sugerido que el equilibrio *proporcional* de excitación-inhibición de las EIN que forman los microcircuitos es mejor indicador tanto de la *ratio* señal-ruido de la señal BOLD como del resultado de estos procesos corticales de *feedback* y *feedforward*. Por sus características anatómico-funcionales, los cambios en el equilibrio de estas redes afectarían directamente al flujo sanguíneo cerebral y, por tanto, a la señal BOLD. De forma determinante, la evidencia muestra que este equilibrio no siempre correlaciona con la actividad de un conjunto de neuronas. En este sentido, podría darse el caso de que se mantuviera un equilibrio recurrente adecuado para afectar al consumo de oxígeno y disparar espontáneamente algunas neuronas y, aun así, que la red o el grupo de neuronas no estuvieran activados. Por ejemplo, en una situación de una gran cantidad de actividad excitatoria e inhibitoria, pese a que las conexiones recurrentes de los circuitos provocarían un gran consumo de oxígeno, el *output* de este grupo de neuronas podría ser 'no disparar', al existir un equilibrio en la excitación-inhibición. Este equilibrio excitación-inhibición de la EIN sería el que guiaría, en última instancia, las respuestas hemodinámicas [5].

Señales de RMf y actividad cerebral

Algunos autores han demostrado, mediante finos paradigmas de estudio en animales no humanos, que la actividad de una neurona se sigue de lo que se conoce como el *dip* inicial, un decremento en sangre oxigenada y aumento de la desoxigenada. Este descenso estaría relacionado con el gasto metabólico de la neurona al activarse y precedería a un aporte extra de sangre, observándose un aumento de la sangre oxigenada, que satisfaría el gasto energético [11]. Esta evidencia vendría a reforzar la idea de que el aumento en el flujo sanguíneo estaría relacionado con la demanda metabólica y, por tanto, con la actividad de las neuronas [12].

Por otra parte, la disposición y el funcionamiento neuronales, en cuanto que nunca registramos la actividad de una única célula, implican entender la señal de RMf como un promedio temporal y espacial de la activación de varias neuronas. Esta lógica es la aplicada por el modelo de transformación lineal. Hipotéticamente, la relación entre actividad y señal está completamente caracterizada por la función de respuesta de impulso hemodinámico (HIRF, por sus siglas en inglés), que hace referencia a la 'respuesta de RMf resultante de un pulso de actividad neuronal breve y espacialmente localizado' [13]. Diversas evidencias de medida simultánea de RMf y actividad neural ponen de manifiesto la eficacia de este modelo [8]. Sin embargo, también hay situaciones que no se ajustan a la HIRF, como, por ejemplo, cuando buscamos predecir los patrones de actividad ante estímulos de larga duración en función de respuestas ante estímulos más cortos [13]. No obstante, para este tipo de situaciones existen estrategias alternativas para modelar la variabilidad de la respuesta BOLD, como el *set* de respuesta de impulso finito [14].

En definitiva, por las cualidades anatómicas y vasculares del cerebro, el estudio de la relación entre la actividad neuronal y la señal hemodinámica es merecedor de una atención especial, debido a su papel central en la interpretación de la RMf. En general, este conjunto de investigaciones resaltan que, si bien la señal BOLD que obtenemos mediante la RMf se relaciona de forma consistente con la actividad de grupos neurales, esta relación es altamente compleja y no conocida al completo. Por ello, es recomendable aplicar cautela a la interpretación de los resultados, así como tener en cuenta dicha complejidad a la hora de hacer inferencias, relacionando diferentes regiones cerebrales con funciones cognitivas de manera simplista.

Aspectos estadísticos

El estudio de los aspectos estadísticos ha tomado especial protagonismo en los últimos años, después de la aparición de algunos estudios muy críticos al respecto [15]. Hay que tener presente que la cuestión principal que debe responder el investigador es si un determinado vóxel o conjunto de vóxeles tiene una actividad diferencial para una tarea *X* comparada con otra *Y*. Para ello, cuenta con una serie temporal de la secuencia de la tarea y otra serie con las secuencias de activación. La labor del investigador es determinar qué áreas son las activadas concretamente por la tarea mediante diferentes cálculos estadísticos. La gran cantidad de datos con los que se trabaja sugiere tomar los análisis con cautela. Además, la gran cantidad de pasos y procesos que se tienen que llevar a cabo para llegar al estadístico final facilita la compresión de por qué estadísticamente la neuroimagen es un campo muy delicado y expuesto a conclusiones cuestionables [16].

El problema del error no independiente: *double dipping*

En 2009, Vul et al [15], sorprendidos ante diferentes resultados de neurociencia social que mostraban altísimas correlaciones entre constructos psicológicos y actividad en zonas cerebrales concretas, decidieron evaluar las técnicas estadísticas de estos artículos. Muchos de estos fueron publicados en revistas de alto impacto y fama, como *Science* [17] o *Nature* [18]. En su artículo, Vul et al [15] sugerían que gran parte de los trabajos revisados con altas correlaciones incurrían en el conocido *double dipping*, cuestionando, por tanto, sus conclusiones. Pero, ¿en qué consiste este error?

El problema del *double dipping* ocurre cuando la medida final que se va a analizar no es independiente del criterio de selección de la muestra. Esto es lo que se conoce como error no independiente [15,19, 20]. A grandes rasgos, en el análisis de neuroimagen hay dos maneras de seleccionar los vóxeles de interés. Por una parte, podemos basarnos en un criterio estrictamente anatómico (por ejemplo, delimitar la amígdala individualmente y seleccionar los datos funcionales restringidos a esta localización anatómica). Por otra parte, se pueden seleccionar los vóxeles a través de un criterio funcional: delimitaremos la actividad de interés a aquellos conjuntos de vóxeles que correlacionen temporalmente con la ejecución de la tarea. El concepto de *double dipping* hace referencia, precisamente, al análisis circular propio de ciertos estudios con RMf en los que primero se hace un análisis selectivo de las zonas activadas y posteriormente se analizan los resultados del mismo conjunto de datos, pero sólo en los vóxeles seleccionados. Diferentes estudios han demostrado cómo esta manera de proceder puede inflar las correlaciones e incluso crear correlaciones significativas a partir de puro ruido estadístico [15,19]. En este sentido, no podemos decir que los resultados no procedan de los datos, pero también es probable que los estemos distorsionando, al traspasar parte de la variabilidad asociada al error de medida con la variabilidad de nuestro propio diseño mediante la selección sesgada de regiones cerebrales. Por tanto, la crítica de estos autores no es a la técnica en sí, sino a ciertos modos de actuar que estarían distorsionando los resultados finales. De hecho, en estos mismos artículos de revisión proponen estrategias para superar el *double dipping*. Ellos asumen la lógica de que una determinada región de interés (ROI) puede responder de forma diferencial ante dos tareas. Una manera de asegurar la independencia estadística de la ROI sería utilizar un nuevo conjunto de datos, diferente al que se utilizó para delimitar la ROI, para comprobar nuestras hipótesis [15,19]. Por tanto, la superación de estas limitaciones estadísticas es simple y sólo requiere la concienciación y el compromiso de los investigadores.

El problema de las inferencias estadísticas

El hecho de que para obtener la RMf se requiera realizar multitud de pasos provoca que la seguridad con la que realizamos nuestras inferencias acerca del resultado disminuya. Por ejemplo, hemos de tener en cuenta que tanto en cada uno de los pasos de preprocesado como en el análisis en sí se pueden estar introduciendo elementos que alteren nuestros patrones de actividad final.

Para evitar, en la medida de lo posible, falsos positivos, normalmente se utilizan estrategias de control asociadas a picos de activación o *clusters*. En ambos casos, el umbral estadístico que hay que superar se corrige por comparaciones múltiples: una corrección restrictiva, como la *familywise error*, tipo Bonferroni, va a limitar la tasa de falsos positivos, pero, por otro lado, va a potenciar los falsos negativos. Otras más laxas, como la *false discovery rate*, irían en sentido contrario [21]. Generalmente, cuando ya se ha corregido, se introduce un umbral de 0,05. Otra opción, más en desuso, es presentar los datos sin corrección por comparaciones múltiples en umbral 0,001 y tamaño de *cluster* 5 o 10 vóxeles. En cualquier caso, lo que se debe tener en cuenta es que, en determinadas situaciones, la elección de un método u otro va a dar lugar a un *output* diferente. De nuevo, esto debe hacer reflexionar sobe la cautela a la hora de interpretar nuestros resultados.

Aspectos teóricos y conceptuales: ¿es la RMf una nueva forma de frenología?

Junto con el gran estallido de publicaciones relacionadas de una u otra forma con la neuroimagen, ha ido ganando protagonismo paralelamente una corriente bastante crítica con los fundamentos teóricos de la técnica. Desde esta perspectiva, se ponen en tela de juicio algunos de los principios sobre los que se asienta la ciencia cognitiva en su conjunto, en general, y la neurociencia (con la RMf como principal representante), en concreto.

En primer lugar, el problema de la localización cerebral en neuroimagen no sería sino una versión moderna del recurrente debate mente-cerebro: hasta qué punto una determinada localización cerebral se podría asociar de forma efectiva con un proceso o función psicológicos. Para los críticos, la neurociencia cognitiva mantiene una postura extremadamente materialista filosóficamente hablando, basada en la ontología monista de que aquellas variaciones que afectaran al dominio psicológico estarían provocadas o se manifestarían en el dominio neurológico [22,23]. En directa conexión, la extremada dificultad de delimitación de conceptos provoca que numerosos constructos psicológicos se solapen y, en ocasiones, vengan a referirse al mismo concepto, pero a través de teorías diferentes [22]. Debido a su objeto de estudio, la psicología como disciplina científica ha tenido que reinventarse a menudo y servirse de estrategias que, de alguna manera, permitieran abordar algo aparentemente interno. Muchas de estas estrategias se han arraigado en la lógica de la ciencia psicológica. Sin embargo, diversos autores cuestionan algunos de estos pilares básicos.

Una de las estrategias utilizada en resonancia es la de sustracción. Supuestamente, las zonas que se activan ante una tarea que no se comparten con la activación base serían las implicadas precisamente en esta tarea. Algunos autores critican la asunción mayoritaria en neurociencia de la 'mera inserción' en la sustracción, mediante la cual se entiende que la interacción entre diferentes procesos cognitivos evocados por una tarea es nula. Sin embargo, las diferencias que se observan al implementar una tarea respecto a la actividad base podrían no sólo explicarse en función del proceso cognitivo teóricamente evocado, sino también por una posible interacción entre éste y los diferentes procesos preexistentes. De hecho, algunos datos sugieren que la mera inserción no es sensible ni a interacciones funcionales ni a fisiológicas, por lo que el uso de esta lógica sustractiva ha de ser aún más cauteloso y parsimonioso para obtener datos suficientemente adecuados [24]. La existencia de manipulaciones no paramétricas y el desarrollo de nuevos acercamientos, como el análisis de patrones multivóxel –*multivoxel pattern analysis* (MVPA) [25]–, que no recae de manera directa en la lógica de la sustracción, suponen estrategias prácticas de superar en cierta medida estas críticas.

¿Pueden superarse estos problemas?

Después de esta revisión de algunas de las limitaciones y de las críticas a la RMf, es importante preguntarse hasta qué punto éstas deben afectar al uso de la técnica y las conclusiones que se deriven de ella. ¿Debemos dejar de utilizar los escáneres de resonancia para abordar asuntos psicológicos? ¿Debe la neurociencia abandonar la técnica y desechar todos los datos que han aparecido en los últimos 20 años? ¿Hay alguna alternativa que no presente limitación? Probablemente, la respuesta no deba ni pueda ser tajante. Numerosos expertos, como Logothetis [5], apuntan en esta dirección: 'a pesar de sus limitaciones, la RMf es hoy por hoy la mejor herramienta que tenemos para aprender sobre la función del cerebro'. Los diversos trabajos poco rigurosos que suelen servir de ejemplo para los detractores de la técnica no son consecuencia de una imperfección intrínseca a ella. Por el contrario, no hacen sino resaltar lo que se ha venido señalando: es necesario un estudio detallado y un entendimiento profundo de los fundamentos de la técnica, de manera que tanto nuestros diseños experimentales como la interpretación que demos a nuestros datos sean lo más cautelosos y certeros posible [26].

Por un lado, ciertas críticas conceptuales probablemente sean demasiado atrevidas y denoten cierto desconocimiento de la actualidad real en el campo, que va más allá de señalar 'frenológicamente' qué área cerebral se encarga de *X* función cerebral [26-29]. Gran parte de estos argumentos comparten, pese a no coincidir en el enfoque, una lógica funcionalista propia de la ciencia cognitiva de la segunda mitad del siglo XX, en la cual se consideraba que los diferentes niveles de análisis de Marr [30] serían independientes, de manera que, efectivamente, el acercamiento biológico no tendría por qué aportar información relevante más que *a posteriori*. Sin embargo, el avance de disciplinas como la neurociencia cognitiva hace pensar que la autonomía de los tres niveles de análisis de Marr no sería tal a la hora de explicar los fenómenos psicológicos humanos. De esta manera, la información biológica dejaría de ser meramente descriptiva para convertirse en explicativa de estos fenómenos [31]. Además, la postura de la inutilidad de la información cerebral en las etiquetas y taxonomías es también cuestionable. Diferentes casos demuestran que esta información no estaría añadiendo confusión al ya de por sí complejo mundo de las taxonomías, sino que ayudaría a valorar su entidad e incluso a crear nuevas clasificaciones [27,29]. Lo más importante sea quizás considerar que cuanta más información converja desde diferentes perspectivas, mayor potencia tendrán nuestras teorías acerca del cerebro y la mente [27]. De hecho, innovadores y recientes trabajos han contribuido enormemente a sintetizar la enorme disparidad de datos de neuroimagen y a integrar la información neural y cognitiva [32]. En definitiva, gran parte de las críticas se deben, en palabras de Hubbard [29], 'a una visión desactualizada de la empresa que el localizacionismo intenta llevar a cabo'. Esto no significa que la RMf esté libre de debates teóricos. No obstante, es necesario recalcar que estos debates no son exclusivos de esta técnica y afectan al campo de la psicología en general.

Por otra parte, en el terreno estadístico, el asunto apunta a ser quizás más polémico. Artículos como el que hemos revisado de Vul et al 15], que planteaba un panorama alarmante en la investigación en neurociencias, han sido duramente criticados. Algunas de estas contracríticas se basan en que, realmente, el famoso *double dipping* no se daría como tal en esta disciplina y, en cambio, sería el análisis del equipo de Vul el que estaría llegando a conclusiones precipitadas sobre la imposibilidad de altas correlaciones y sobre el error no independiente [33,34]. Quizás más preocupante que este debate, que parece tener una solución relativamente sencilla, es el hecho de que el número de ocasiones para perder la rigurosidad estadística en un estudio de resonancia es peligrosamente alto. Como ejemplo de esta potencial variabilidad, diferentes metaanálisis muestran una considerable inconsistencia de resultados. El problema es recursivo: controlar esta inconsistencia es muy complicado, debido a que sus causas pueden ser muy diversas. Incluso si aislamos el efecto del factor humano, hay evidencia de que se pueden seguir produciendo alteraciones en los datos analizados con un mismo programa, por ejemplo, en función del sistema operativo o de la versión del programa utilizados [35]. En definitiva, encontramos ciertas diferencias entre las limitaciones que se han revisado. Aspectos como el *double dipping* o el método de corrección dependen completamente del trabajo del investigador y se pueden evitar fácilmente. En concreto, el problema de los umbrales de corrección se controla mediante la utilización de criterios más o menos explícitos en la comunidad científica. En este sentido, la utilización de la corrección de Bonferroni es bastante inusual en la actualidad, ya que su alto grado de restricción suele estar acompañado de muchos falsos negativos. Por ello, lo habitual es utilizar correcciones intermedias, como el tamaño de *cluster* o las simulaciones Montecarlo. No obstante, otra serie de fuentes de error de naturaleza más inherente a la lógica estadística han de ser objeto de especial cuidado. La gran cantidad de decisiones que tienen que tomarse a lo largo el análisis requieren que el acercamiento a los datos de la RMf se produzca con el conocimiento y la parsimonia científica adecuados. El objetivo del investigador debería ser que sus resultados fueran lo más válidos y objetivos posible, por lo que el control del método y del análisis es de especial importancia a la hora de utilizar la técnica de resonancia [36]. En este sentido, apostar por el trabajo en equipos multidisciplinares que cuenten con personal cualificado en asuntos estadísticos parece ser una opción bastante óptima.

La neurociencia, seguramente por su juventud, ha demostrado ser una disciplina en la que se producen avances significativos de forma muy rápida. Las técnicas de neuroimagen son un claro ejemplo de esto. Diferentes estrategias propuestas en los últimos años suponen novedosas formas de superar algunas de estas críticas que hemos revisado. Por ejemplo, en el MVPA se evitaría la sustracción de imágenes mediante la utilización de algoritmos entrenados en la detección de patrones de activación [37]. Por otro lado, la aparición de los análisis de actividad cerebral en reposo supone una nueva estrategia que no incurriría en ciertos problemas clásicos (aunque añade otros nuevos; véase, por ejemplo, [38]). Mediante esta técnica, en la que se estudian los patrones de actividad coherente de diferentes zonas del cerebro en reposo (es decir, sin presentar ninguna tarea), se han observado redes de comunicación entre áreas que se solapan parcialmente con identificados clásicamente ante la realización de diversas tareas [39]. Este importante avance no sólo evita el problema de la inserción pura en la sustracción; además, supone alejarse de explicaciones *ad hoc* de nuestras activaciones y podría permitir, quizás, un comienzo en la clarificación del problema de las taxonomías psicológicas.

Conclusiones

Pensar que la RMf nos permite leer literalmente la mente del sujeto es igual de precipitado que desechar por completo la neuroimagen por considerarla una especie de frenología moderna sin ningún tipo de contenido de interés. Parafraseando a Logothetis [5], seguramente, ambos tipos de extremos nazcan de una falta de conocimiento riguroso del funcionamiento y de sus bases teórico-técnicas. Es a partir de esos contextos de donde surgen acercamientos que seguramente estén fallando ya desde el planteamiento de las preguntas que buscan responder a través de la RMf [40]. Debido a la multitud de aspectos que han de tenerse en cuenta, de nuevo, es interesante el concepto de equipos multidisciplinares formados por psicólogos, ingenieros, estadísticos, neurólogos, etc., que van a potenciar un mayor control en cada uno de sus respectivos campos.

El mundo de la neuroimagen es un mundo complejo, difícil de abordar y requiere una alta dedicación. No obstante, también es un mundo en el que se están produciendo, a una gran velocidad, avances de gran importancia. En cualquier caso, lo que parece innegable es el surgimiento de aproximaciones cada vez más avanzadas que quizás no contenten a los grandes detractores del campo, pero que, sin duda, están construyendo las ideas que tendremos en un futuro a medio-largo plazo sobre la hasta ahora esquiva relación entre nuestro órgano físico cerebral y toda nuestra subjetivamente única psique.

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Functional magnetic resonance imaging: a critical analysis of its technical, statistical and theoretical implications in human neuroscience

Introduction. The use of functional magnetic resonance imaging (fMRI) has represented an important step forward for the neurosciences. Nevertheless, it has also been subject to rather a lot of criticism.

Aim. To study the most widespread criticism against fMRI, so that researchers who are starting to use it may know the different elements that must be taken into account to be able to take a suitable approach to this technique.

Development. The fact that fMRI allows brain activity to be observed makes it a very attractive and useful tool, and its use has grown exponentially since the last decade of the 20th century. At the same time, criticism against its use has become especially fierce. Most of this scepticism can be classified into aspects related with the technique and physiology, the analysis of data and their theoretical interpretation. In this study we will review the main arguments defended in each of these three areas, as well as looking at whether they are well-founded or not. Additionally, this work is also intended as a reference for novel researchers when it comes to identifying elements that must be taken into account as they approach fMRI.

Conclusions. Despite the fact that fMRI is one of the most interesting options for observing the brain available today, its correct utilisation requires a great deal of control and knowledge. Even so, today most of the criticism it receives no longer has any solid foundation on which to stand.

Key words. Behaviour. Cognition. Cognitive neuroscience. Functional magnetic resonance. Neuroimaging. Neuroscience.

Apéndice 3

González-García, C., Mas-Herrero, E., de Diego-Balaguer, R., & Ruz, M. (2016). Task-specific preparatory neural activations in low-interference contexts. *Brain Structure and Function*, 221(8), 3997-4006. https://doi.org/10.1007/s00429-015-1141-5

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ORIGINAL ARTICLE

Task-specific preparatory neural activations in low-interference contexts

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Abstract How the brain prepares for forthcoming events is a pivotal question in human neuroscience. In the last years, several studies have suggested that expectations of perceiving upcoming stimuli engage relevant perceptual areas. Similarly, some experiments manipulating the task to be performed with targets have also found pre-activations in task-related brain areas. However, the usual configuration of this type of paradigms entails high levels of interference and/or working memory load, together with a small set of target stimuli. We designed a cued task paradigm in which interference was reduced to a minimum, as evidenced by behavioral indices of performance, and that included a high number of targets to avoid their anticipation. This was achieved using a large set of univalent target stimuli preceded by fully valid cues in a functional magnetic resonance imaging experiment. We found category-specific patterns of activity in which semantic cues engaged the left inferior frontal gyrus whereas spatial cues preactivated the right superior parietal lobe. Together with functional connectivity analyses, the activation maps showed the specific involvement of semantic and spatial processes upon the presentation of the cues that are coherent with previous literature. Our results thus suggest that even in contexts of low interference that prevent the anticipation of specific targets, our brain takes advantage of current information to deal with upcoming demands.

Keywords Preparation · Cognitive control · Interference · Task set

Introduction

One of the most adaptive human abilities is to plan and control future behavior based on goals. Rather than merely responding to sensory stimulation in an automatic manner, our brain has the capacity to enter task states that guide the processing of relevant stimuli according to behavioral requirements (e.g., Gilbert and Sigman 2007). Preparation, that is, the anticipation of a given context before it occurs (Brass and von Cramon 2002, 2004; Bode and Haynes 2009), is an important process underlying this ability. As an example, imagine you are expecting a call from your boss and another from a close friend. In this scenario, reading the name of the caller on the screen of the ringing phone would allow you to anticipate your response in a context-dependent manner. In a related area of research (Summerfield and Egner 2009), predictive coding theories propose that our perception depends on iterative processes between bottom-up and top-down information along the cortical hierarchy (Friston 2005). At each step of this hierarchy, top-down expectations are met with bottom-up sensory information that updates the expected input and reduces prediction errors.

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Our knowledge of how top-down templates are implemented in the brain has improved substantially in recent years, due in part to the progressive refinement in neuroimaging methods and analyses. In particular, event-related functional magnetic resonance imaging (fMRI) allows the separation of the brain activations related to cues, which can initiate top-down states, and to the subsequent targets, which are processed according to task requirements. Research in the field of selective attention has suggested that top-down settings are able to modify activity at different stages of information processing according to task goals (e.g., Baldauf and Desimone 2014; Kastner and Pinsk 2004). Selective attentional modulations may increase the tonic state of relevant brain areas before the stimulation is presented (e.g., Ruz and Nobre 2008a), which is accompanied by further increases in responses evoked by targets (e.g., Chawla et al. 1999). These modulations may reflect in part the filtering of irrelevant information (Kastner and Pinsk 2004), and/or enhancement of task-relevant processes (e.g., Corbetta et al. 1990; Ruz et al. 2005; Ruz and Nobre 2008b; Wylie et al. 2006).

In task cueing paradigms (for other approaches, see Manelis and Reder 2013), participants have to prepare for alternating tasks that imply different rules. A large amount of studies has pointed to the prefrontal cortex (PFC) as a key area for set preparation (see Sakai 2008, for a review) within a more general frontoparietal control network involved in task implementation (Ruge et al. 2013). Although the majority of the studies have focused on the difference between switch and non-switch trials, other investigations highlight the specificity of preactivations for certain types of task sets. On a seminal paper, Sakai and Passingham (2003) showed how in a working memory (WM) task in which participants were cued in advance to hold in mind and manipulate spatial vs. semantic material, the preparatory cues modulated the pattern of connectivity between the anterior PFC and other frontal structures, suggesting a domain-specific role of the latter during the preparation stage. In addition, these authors showed that semantic cues elicited preactivation of the left inferior frontal gyrus (LIFG) and temporal areas (superior and middle temporal gyrus), whereas the superior frontal sulcus and the superior parietal lobe (SPL) were selective for spatial cues. This line of results, in which goal-related activity during task preparation is observed within and outside the core control network, has been supported by further evidence (e.g., Sakai and Passingham 2006; Donohue et al. 2008; Yamagata et al. 2012). Altogether, neuroimaging evidence suggests that different brain regions and networks working at different levels of specificity support the brain's ability to prepare for forthcoming events.

However, different sources of interference, such as target ambiguity, invalid cues or cue-target compounds, require increased cognitive control and may affect specific preparatory activity, a hypothesis that has been not been tested yet. For instance, the use of bivalent targets in task-switching experiments, that is, when the same target stimulus can be processed according to either task, has been related to higher switching costs (e.g., Kiesel et al. 2010). In a typical task cueing paradigm, targets are common across tasks, and thus the ignored dimension triggers the activation of the irrelevant information, therefore, generating interference. For instance, in Shi et al. (2014), a cue signaled whether participants should perform a face or a number task with the next target, which was a composition of a face and a superimposed number. These authors found that after a face task trial, regardless of which task had to be performed on the following trial, there was residual activity in brain areas associated with face processing. Likewise, they found a significant positive correlation between the amount of this residual activity and switching costs. This residual activity in switch trails has been attributed to the competition between the two tasks to gain control (Wylie et al. 2006). In bivalent contexts, compared to univalent ones, control demands are high due to interference between tasks, and thus the need for selective attention is increased (e.g., Stokes et al. 2013). In fact, Yeung et al. (2006) found that task-set inertia in task-switching paradigms accounts for a large portion of switching effects, which, crucially, affected both frontoparietal and category-specific preparatory activations.

Evidence for category-specific preactivations with univalent targets (i.e., each task is linked to a specific type of target) also comes from visual attention studies, in which participants are prompted to classify stimuli in categories rather than to perform a given task with it. For instance, Puri et al. (2009) used a task in which participants had to prepare for perceiving faces or houses images, cued in a 70 % of trials by a valid cue (e.g., the word “FACE” in a face image trial). These authors found that the mere cuing of a category (face or house) activated the associated perceptual brain region (fusiform face area, FFA, or parahipocampal cortex, PPC, respectively) prior to the presentation of the image and enhanced the target-related activity in these areas. Moreover, the magnitude of the preactivations in these category-specific areas correlated with the activity of the aforementioned frontoparietal network. This effect supported the idea of a top-down modulation from this network towards sensory cortices (see also Esterman and Yantis 2009). In this study, however, a percentage of the cues was invalid, which also generates interference. When a cue is valid, that is, when it adequately signals the upcoming task, it engages attentional mechanisms that allow for a better response to the next target. As for invalid cues, interference arises due to the mismatch between the cued and the actual task, which requires a disengagement of attentional resources upon target presentation. As seen with other sources of interference, this may influence the extent and selectivity of preparatory activity (De Baene and Brass 2014). Interestingly, some authors have shown the utility of using only valid cues to reduce the interfering task-set inertia in univalent contexts (Elchlepp et al. 2012). Therefore, despite suggestive evidence of cue-related activations with univalent targets, the effect of cue validity on these preparatory mechanisms is still unknown.

Moreover, an additional source of potential selectivity of preparatory activity in switching experiments is the use of a small set of stimuli. This allows for the creation of cue-target compounds (explicit responses encoded in episodic memory for a given cue-target conjoint; Logan and Bundesen 2004), which could trigger cue-related activation due to repeated association of specific cues and targets (e.g., the cue "red circle" always signals a square or triangle target, whereas the cue "green circle" is linked to a blue or yellow shape). Moreover, using small set of target stimuli allows for the imagination and rehearsal of the forthcoming task upon the presentation of the cue (Klauer and Zhao 2004). These strategies involve modality-related working memory processes, such as articulation for phonological demands, or visual imagery for visual tasks (Baddeley 2003). Thus, when few visual stimuli are used, as in the case of most studies revised here (e.g., Esterman and Yantis 2009), visual imagery entails additional working memory demands, which usually engage selective maintenance activity in the prefrontal cortex (e.g., Curtis and D'Esposito 2003), potentially confounding task and item preparatory activity.

In sum, previous studies have used task-switching paradigms that imply different sources of interference. Importantly, these can affect the consistency of the neural correlates of preparatory mechanisms, since interference affects the interplay between top-down and bottom-up information. The extent to which task-specific preparatory activity also takes place in contexts of low interference remains unknown. The aim of the present study was to investigate the existence of specific preparatory activity in a paradigm designed to keep interference between tasks and item-specific visual anticipation to a minimum. To do so, we employed a task in which (1) targets were univalent and fully distinct, (2) cues always provided valid information, (3) a large set of targets was used, to prevent visual imagery and avoid cue-target compounds. Cues were symbolic and asked participants to perform within-category classifications. Although we could have used different target modalities, such as visual and auditory, to reduce interference even more, we chose two visual categories, semantic and spatial, that are "maximally distinct" (Ruge et al. 2013) and whose specific activation and connectivity patterns are well mapped (e.g., Sakai and Passingham 2003). Our approach allowed us to study a consistent pattern of activation and connectivity associated with category-specific preparatory processes under conditions of low interference.

Materials and methods

Participants

Twenty-four participants (16 females; mean age 22; range 19–26) took part in the experiment. All participants reported normal or corrected-to-normal vision and no history of neurological disorders. They all signed a consent form approved by the local ethics committee and received money in exchange of their participation.

Apparatus and stimuli

The stimuli consisted of 56 concrete noun words (average number of letters 5.7, range 5–7) and 56 different overlapped rectangles and oval shapes containing leftward or rightward oriented lines (see Fig. 1). Half of the words represented natural items (e.g., agatha) and the other half referred to man-made objects (e.g., fork). The rectangle and oval overlapped figures contained lines in the same direction in half of the shapes and in opposite directions in the other half. Two different squares, colored in blue and green, were used as cues. A PC running Presentation 0.70 displayed the stimuli through MR-compatible goggles.

Design and procedure

Both tasks were performed in an interleaved single run. The (blue, green) cue (100 % valid) instructed participants

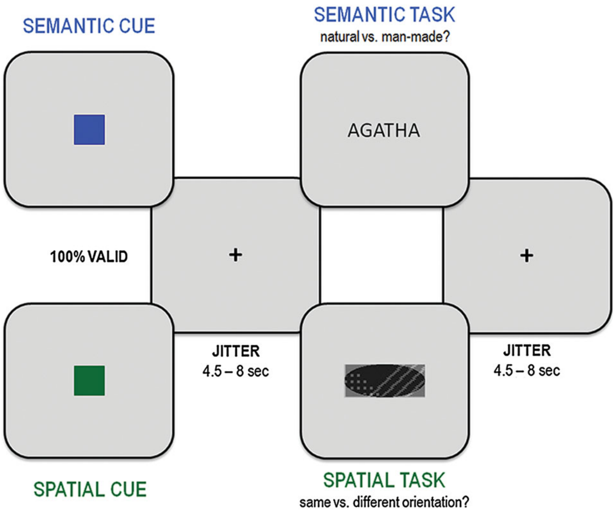

Fig. 1 Sequence of events in a trial for the event-related fMRI design

on a trial-by-trial basis about the task they had to perform on the upcoming target (either a word or a complex shape). They had to judge the semantic content of the words (decide whether the items represented something natural or man-made) or the spatial orientation of the lines in the complex shapes (whether the lines of the superimposed rectangle and oval were oriented in the same or in the opposite direction). Participants were encouraged to respond as accurately and as fast as possible. In addition, they were asked to use the cue to prepare as much as possible before target onset, as this would help them to respond more efficiently. To encourage this preparation, before the experiment participants were informed that the three persons with the highest performance scores (taking into account both accuracy and speed) would be rewarded with 25 Euros extra.

The association between cues and tasks, as well as the response options, was counterbalanced across participants. In the event-related run (50 min approximately), the delays between cue and target, and between trials, were jittered to allow for the deconvolution of cue- and target-related signals. Each trial comprised the following events (see Fig. 1). A cue was flashed in the center of the screen for 500 ms, followed by an interval displaying the fixation point with a 4.5–8 s duration that varied randomly in steps of 500 ms (mean 6.25 s). The target then replaced the fixation point for 500 ms, after which another variable interval was presented, with the same structure as the previous one. On average, a trial lasted 13.5 s. In total, there were 224 trials (112 per condition), ran in a pseudo-random order that presented all items once before displaying them for the second time (every item was used twice) and thus avoided immediate item repetitions.

During the whole experiment, participants used the index and middle fingers of their right hand to make speeded discrimination responses to targets by pressing one of two buttons on a custom-made MRI-compatible button box. Before performing the task in the scanner, participants completed a short training session with a different set of stimuli to become familiar with the tasks.

Prior to the fMRI experiment, we conducted a behavioral pilot study to ensure that with the current design cues received attention and participants used them to prepare in advance. All details of the design and stimuli were the same except cues were invalid in 20 % of the trials.

Data acquisition and analysis

Magnetic-resonance images were acquired using a 3T Trio scanner at the Hospital Clinic of Barcelona (Spain). Functional images were obtained with a one-shot T2*-weighted echo planar imaging (EPI) sequence [time until echo (TE) = 29 ms, flip angle = 80°, repetition time (TR) = 2 s]. Thirty-eight interleaved sagittal slices with a thickness of 3.0 mm (no gap) covered the entire brain (64 × 64 matrix with a field of view of 240 mm, voxel size of 3 × 3 × 3 mm). The event-related experiment was performed in one run consisting of 1540 volumes. The first 5 images were discarded to allow for saturation of the signal. In addition, we acquired a standard structural image of each participant using a high-resolution T1-weighted sequence (TR = 2300 ms; TE = 2.98 ms; 1 × 1 mm in-plane resolution and 1 slice thickness).

We used SPM8 (http://www.fil.ion.ucl.ac.uk/spm) to preprocess and analyze the images. First, we used slice timing to correct for differences in the time of slice acquisitions. Images were then realigned and unwarped using a least-squares approach and a six-parameter (rigid body) spatial transformation to correct for motion artifacts. Afterwards, images were normalized to the standard EPI template included in SPM8. Images were spatially smoothed using an 8 mm full-width at half-maximum isotropic Gaussian kernel. A 128 s high-pass filter was used to remove low-frequency artifacts.

Statistical analysis was performed with a General Linear Model for each participant with corrections for serial autocorrelations using the AR(1) model. The model included regressors for the cues and targets in both switch and non-switch situations, which were convolved with the standard hemodynamic response function. Duration and onset vectors for each condition were introduced as regressors into a standard General Linear Model (GLM). The two different cues (Semantic, Spatial) were modeled as events with a duration that encompassed the whole cue-target interval, which allowed us to capture the sustained anticipatory activity generated by each type of cue. Targets were modeled as events with zero duration. Jittered intervals between trials were used as implicit baseline, and trials with errors and missing responses were grouped together as separate events with an extended duration for the whole trial (encompassing both cue and targets). Contrasts of interest (i.e., cues vs. baseline; semantic vs. spatial cues: CUE_SEM > CUE_SPA and viceversa; semantic vs. spatial targets: TARGET_SEM > TARGET SPA and viceversa; switch vs. non-switch cues and targets) were obtained for each participant and then entered into a second-level analysis, where t tests were used to contrast conditions. Only clusters surviving a family wise error (FWE) correction thresholded at a 0.05 cluster-level (initial uncorrected cluster-forming threshold was $p < 0.001$) are reported. In the figures, we used Caret software (Van Essen 2005) to project the images on to inflated PALS surface (population-average, landmark- and surface-based) and help visualization.

General and specific cue- and target-related activations

We first identified the brain areas that were engaged by cues (contrast CUES > BASELINE) to map the preactivations across tasks. Then, we sought to isolate the regions that were engaged by each cue type in a task-selective manner. For this, we calculated the contrasts CUE_SEM > CUE_SPA and vice versa, to obtain category-specific clusters. Additionally, we used results from the contrasts TARGET_SEM > TARGET_SPA and vice versa to look for category-specific activity at the target period. To further explore whether target-related clusters were preactivated at the cue stage, we conducted a conjunction analysis (Nichols et al. 2005) to test which precise brain areas were active in both cue and target periods of a given task. This analysis allowed us to look for clusters specific to each task that were active both in the cue and the target periods. For conjunction analyses, we performed one-way ANOVAs using first-level contrast images of interest. Only conjunction clusters surviving an MS/CN test (Minimum Statistic compared to the Conjunction Null; Nichols et al. 2005) are reported.

Psychophysiological interactions

To assess the networks involved in the advance preparation to perform semantic vs. spatial computations, we conducted a psychophysiological interaction analysis (PPI; Friston et al. 1997) using SPM8. The GLM analysis described above identified the left inferior frontal gyrus (LIFG; −48, 26, 1) and the right superior parietal lobe (RSPL; 24, −67, 52) as key regions of preactivation for the semantic and spatial cues. These two coordinates were the center of 6-mm radius spherical seeds in the two PPI analyses during the preparation period. A first-level GLM analysis was then performed using the specific ROI time course, the psychological variable (cue type) and the interaction term (PPI) obtained in SPM8 as regressors. After obtaining a contrast image of the interaction for each subject, we performed a second-level t test analysis. Clusters surviving the statistical threshold corresponded to areas whose temporal activation pattern correlated with that of the ROIs, upon presentation of a given cue.

Results

Behavioral

Six participants performed a behavioral pilot study that used univalent targets but included cue validity as a factor. Results showed that whereas accuracy did not change as a function of validity ($F < 1$), participants were faster on valid ($M = 773$ ms, SD = 160) than on invalid ($M = 860$ ms, SD = 186) trials, $F_{1,5} = 9.37$, $p < 0.05$. This significant validity effect indicates that participants paid attention to the cues and prepared to respond accordingly, even though these were not fully reliable and all targets were associated unequivocally with only one task.

During the fMRI session, accuracy analyses showed a main effect of task, as participants were more accurate in the perceptual (97 %) than in the semantic task (94 %), $F_{1,23} = 10.1$, $p < 0.01$ (all other Fs ≤ 1). The ANOVA on reaction times (RT) showed a main effect of task, $F_{1,23} = 137.41$, $p < 0.001$, as RT were faster in the spatial (751.9 ms) than in the semantic (918.4 ms) condition. Neither the main effect of switch, $F_{1,23} = 1.19$, $p > 0.28$, nor the interaction between the two factors, $F_{1,23} = 2.8$, $p > 0.1$, were significant.

GLM

First, we used the CUES > BASELINE contrast to look for preparation across tasks during the cue period (Fig. 2, left panel). We found strong activation in several regions, including right (33, 53, 28; $k = 131$) and left (−27, 38, 28; $k = 177$) anterior lateral prefrontal cortex (PFC, BA 10), right mid-dorsolateral PFC (48, 14, 22; $k = 23$), posterior cingulate cortex (PCC, −3, −25, 28; $k = 783$), supplementary motor area (SMA, −6, 5, 58; $k = 513$), bilateral insula (−33, 20, 1, and 31, 17, 1; $k = 228$), thalamus (−3, −22, 1; $k = 446$), left somatosensory cortex (−42, −31, 61; $k = 83$), right (30, −52, 52; $k = 40$) and left superior parietal lobe (SPL, −27, −58, 55; $k = 456$), and visual areas such as BA 17−18 (−27, −97, −8; $k = 213$) and BA 19 (36, −88, −8; $k = 255$).

Afterward, we located brain areas engaged by category-specific target processing, which included those commonly reported during semantic and spatial computations. Target words (TARGET_SEM > TARGET_SPA) activated a typical left-lateralized language network, including the left inferior frontal gyrus (IFG, −42, 26, −11; $k = 704$), left superior frontal gyrus (−3, 14, 52; $k = 153$) and the left fusiform gyrus (−54, −49, −17; $k = 100$), as well as the right IFG (30, 29, −1; $k = 315$), right dorsolateral prefrontal cortex (RDLPF; 54, 32, 31; $k = 93$), and occipital regions (−6, −85, 10; $k = 169$). On the other hand, spatial targets (TARGET_SPA > TARGET_SEM) engaged different parietal regions such as the right SPL (12, −73, 58; $k = 234$) and the left inferior parietal lobe (IPL, −33, −91, 19; $k = 119$), as well as the right fusiform gyrus (36, −56, −12; $k = 205$) and BA 19 (36, −85, 13; $k = 357$).

The analysis of semantic cues (CUE_SEM > CUE_SPA) revealed a large cluster of activation in the LIFG

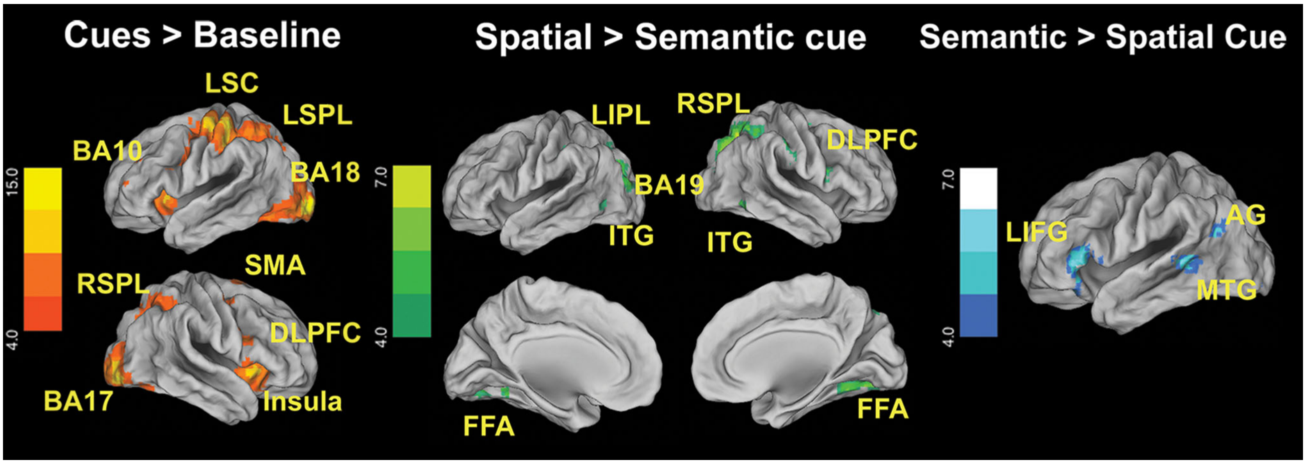

Fig. 2 Activation common for cues across tasks (*left*), and specific for spatial (*middle*) and semantic (*right*) cues. The Cues > Baseline contrast revealed significant activation in bilateral BA 10 (brodmann area 10), right DLPFC (dorsolateral prefrontal cortex), bilateral insula, SMA (supplementary motor area), LSC (left somatosensory cortex), bilateral SPL (superior parietal lobe), BA 17 (brodmann area 17) and BA 18 (brodmann area 18). Spatial cues engaged right DLPFC, RSPL, LIPL (left inferior parietal lobe), bilateral ITG (inferior temporal gyrus), bilateral FFA (fusiform face area) and BA 19 (brodmann area 19). Semantic cues activated the LIFG (left inferior frontal gyrus), left MTG (middle temporal gyrus) and left AG (angular gyrus). *Scales* represent peaks *t* values

(−48, 26, 1; $k = 373$), as well as in other language-related areas (see Fig. 2, right panel), such as the left middle temporal gyrus (BA22; −54, −43, 1; $k = 151$) and the left angular gyrus (BA 39; −42, −64, 25; $k = 151$). An additional cluster was found in the right middle occipital gyrus (BA 19; 33, −97, −8; $k = 68$). For spatial cues (CUE_SPA > CUE_SEM), the statistical map depicted a pattern of activation in areas related to spatial processing (see Fig. 2, middle panel), namely a large cluster in the parietal lobe, with a local maxima at the RSPL (24, −67, 52; $k = 759$), and LIPL (−33, −37, 43; $k = 147$), as well as in bilateral inferior temporal gyri (−51, −67, −2; $k = 84$; and 54, −61, −11; $k = 68$) and bilateral fusiform gyri (−27, 52, −14; $k = 141$; and 30, −55, −11; $k = 182$). Additionally, we found activations in bilateral BA 19 regions (−33, −86, 19; $k = 354$; and 36, −85, 22; $k = 59$) and in the RDLPFC (51, 8, 19; $k = 127$). However, although these areas showed higher levels of activation for one of the tasks, it could be the case that the other task also engaged them although to a lesser degree. To rule out this scenario, we selected the peak clusters in both tasks (RSPL for the spatial and LIFG for the semantic task) to create ROIs. Then, we used these two ROIs to query activity in the opposite task contrasts (e.g., for the RSPL ROI, CUE_SEM > CUE_PER and Cue_SEM > BASELINE). This analysis did not yield significant results for any of the contrasts even when the correction was lowered to $p < 0.1$ uncorrected.

None of the contrasts involving the switch factor (i.e., switch vs. non-switch cues and targets) survived the FWE threshold (neither a $p < 0.001$ uncorrected, 10 voxel-extent threshold). To confirm the absence of switching effects, we conducted ROI-based (FWE corrected) comparison of Switch > Repeat trials for all clusters identified in the CUES > BASELINE contrast. This did not yield significant results even after lowering the correction to an uncorrected 0.1 cluster-level threshold. We also computed the Switch > Repeat contrast for each task separately in the regions showing the strongest task-specific preparatory activation effects (i.e., IFG and SPL). Again, no significant effects were found even at an uncorrected $p < 0.1$ cluster-level threshold.

Conjunction analysis

To isolate the brain areas involved in target processing that were pre-activated by preparatory cues, we performed a conjunction analysis ([CUE_SEM > CUE_SPA] > [TARGET_SEM > TARGET_SPA] and vice versa) as described in Methods section. A large portion of the LIFG (−51, 29, −2; $k = 365$) was engaged by both semantic cues and word targets (Fig. 3, right panel). Spatial targets (Fig. 3, left panel), on the other hand, activated the RSPL (24, −67, 49: $k = 112$), the left BA 19 (−33, −88, 16; $k = 190$), and the right fusiform gyrus (30, −58, −14; $k = 154$).

PPI analyses

The pattern of connections of the two key regions during the preparation period changed according to the task that participants were expecting (Fig. 4). Preparing to perform a semantic task increased the connectivity of the LIFG with the anterior part of the left insula (−36, 26, 4; $k = 110$), the SMA (−3, 17, 52, $k = 185$) and the left SPL (−33, −49, 52; $k = 469$). The LIFG also increased its

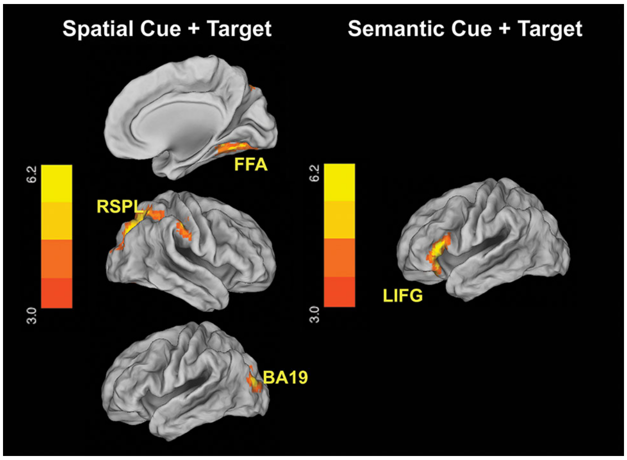

Fig. 3 Cue and target conjunction results for spatial (*left*) and semantic (*right*) trials. The right SPL (superior parietal lobe), right FFA (fusiform face area) and left BA19 (brodmann area 19) were active both for spatial cues and targets, whereas the left IFG (left inferior frontal gyrus) was the only area engaged during semantic cues and targets. *Scales* represent peaks *t* values

connectivity with a large perceptual cluster ($k = 581$) including the left fusiform gyrus in the vicinity of the Visual Word Form Area (−42, −58, −14; McCandliss et al. 2003), as well as left and right BA 18 (−24, −94, −8; $k = 99$; 24, −97, −5; $k = 92$).

On the other hand, preparation to perform a spatial task enhanced the connectivity between the RSPL and neighboring regions such as the IPL (48, −31, 55; $k = 118$) as well as homologous areas in the left hemisphere (−39, −43, 52; $k = 189$). Additionally, the RSPL also increased its coupling with several occipital regions such as the left and right BA 19 (−33, −73, −17; $k = 121$; 36, −91, 13; $k = 61$), and posterior right temporal areas (57, −61, −14; $k = 110$).

Discussion

The current investigation revealed that expectations about an upcoming stimulus category activate some of the brain regions that are involved in target processing later on. These areas include the LIFG for linguistic expectations and the RSPL for abstract figures, which suggests that key regions for semantic and spatial processing (e.g., Jefferies 2013; Husain and Nachev 2007) are already engaged when expecting to encounter items belonging to these categories. Crucially, these activations were found in a setting with minimal interference, in which a large set of univalent targets were preceded by fully valid cues. The different manipulations we introduced were able to abolish switching effects (both at behavioral and neural levels). The use of univalent targets alleviates interference between tasks (Kiesel et al. 2010), probably by decreasing automatic task inertia in the patterns of activations (Yeung et al. 2006). Also, we avoided the use of invalid cues as they increase interference, a potential source of switching costs (Yeung et al. 2006). Although the use of 100 % valid cues could impair the mobilization of attentional resources during the preparatory stage, it has also been suggested that invalid cues could hinder preparatory activations by minimizing the perceived utility of the cue (Wendt et al. 2012). Crucially, our behavioral pilot data showed validity effects in a setting where cues were even less likely to be processed than in the fMRI paradigm, given the presence of 20 % of invalid cues. Still, the fMRI patterns strongly suggest that cues preactivated brain regions relevant for subsequent target-specific processing.

Preparing in advance for upcoming demands is a well-documented human ability. This ability relies on different brain networks, which include a frontoparietal one as the most prominent (Ruge et al. 2013). This network is not only linked to preparatory processes but also to cognitive control and attention in general (e.g., Corbetta et al. 2008). Since preparation depends on control mechanisms, the implication of frontoparietal nodes seems quite coherent. The present study adds to previous research about the neural correlates of this process by finding task-specific brain patterns of both activity and connectivity under conditions of low interference.

Regarding activations common to cues, we found significant clusters in anterior and posterior parts of the PFC and premotor areas, and generic areas of maintenance of

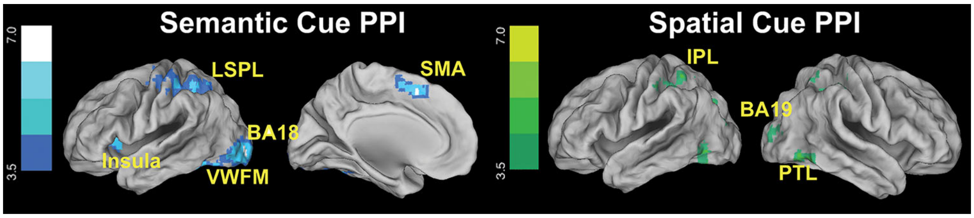

Fig. 4 PPI analysis results for semantic (*left*) and spatial (*right*) cues. Upon the presentation of a semantic cue, the seed (LIFG; left inferior frontal gyrus) enhanced its connectivity with the left Insula, SMA (supplementary motor area), left SPL (superior parietal lobe), left fusiform gyrus (visual word form area) and BA 18 (brodmann area 18). On the other hand, the spatial seed (RSPL; right superior parietal lobe) increased its connectivity with the left IPL (inferior parietal lobe), bilateral PTL (posterior temporal lobe) and BA 19 (brodmann area 19) during spatial cue processing. *Scales* represent peaks *t* values

control sets (i.e., the insula; Dosenbach et al. 2008), and some motor and visual regions. Anterior frontal activations have been related to active maintenance of task sets, which could potentially increase WM load in long cue-target interval designs due to anticipatory visual imagery when a small set of stimuli is used (Baddeley 2003; Ruge et al. 2013). However, we used a wide variety of stimuli that made not possible for participants to image them in advance, thus abolishing the impact of anticipatory item maintenance during the cue-target interval. Moreover, in our task participants could not form explicit cue-target compounds, and thus they could not prepare direct responses upon the presentation of the cue. The implication of the mid-dorsolateral PFC near the Inferior Frontal Junction together with premotor areas is consistent with the activation of the abstract (not item-related) task sets (Ruge et al. 2013; Baldauf and Desimone 2014) needed. On the other hand, our pattern of results seems to be in line with previous studies on switch probability, which suggest that differences between switch and non-switch trials might be related to particular preparatory strategies. De Baene and Brass (2013, 2014) revealed a dissociation between strategy-dependent and independent areas in preparation, in which the LPFC, the LIPL and the left MTG seemed to be involved in low switch-probability contexts (probably reflecting the increased control required in unexpected switch trials), whereas the preSMA and the SPL were insensitive to the probability-related strategy. A relatively high switch probability scenario such as ours (i.e., 50 % switch trials) may have reduced the activation of the LFPC, LIPL and left MTG, since the strategy could have moved "to an intermediate neutral control state" (De Baene and Brass 2013). Interestingly, the high switch-probability scenario is thought to erase both neural and behavioral switch-specific results. This, together with the other experimental manipulations that reduced interference between tasks, could help explain the absence of switching effects in our results.

Furthermore, the GLM revealed coherent-specific activity for each cue category. The activation of the rostral LIFG has often been related to the selection of task-relevant semantic information (e.g., Fiez 1997; Wagner et al. 2001). Our experiment replicates previous findings (Sakai and Passingham 2003) showing that this brain region is engaged by semantic cues, before any target word is presented. This represents further evidence for the role of this area in maintaining a preparatory state for subsequent semantic processing. Our analyses showed that semantic cues also activated the middle temporal lobe and the angular gyrus. These areas, together with the LIFG, are thought to conform a crucial network for semantic control (Binder et al. 1997; Price 2000; Jefferies 2013). Some authors (Noonan et al. 2013) propose that the middle temporal gyrus tunes the semantic processing to the appropriate aspects required by the context, while the angular gyrus may be in charge of selecting goal-related semantic features (Jefferies 2013). In addition, conjunction analysis revealed that the LIFG was activated both during the semantic cue and during word targets, which support its role in semantic-controlled processes. However, the other two areas contributed exclusively upon the presentation of the cue, suggesting that these control processes might help LIFG in facing semantic stimuli successfully by contributing to an adequate preparatory state before target appearance.

Additionally, the pattern of connectivity of the LIFG showed how even before the presentation of the word, this area connected with others such as visual regions in the vicinity of the Visual Word Form Area. This region is a key component of visual word recognition due to its role in bridging word perceptual aspects with higher order semantic information (McCandliss et al. 2003). On the other hand, the LIFG was also functionally coupled with the insula, having a core role in language processing (see Ardila et al. 2014 for a recent review). Pivotal theories (e.g., Dosenbach et al. 2008) argue the additional involvement of the insula and the frontal operculum in control processes. In fact, the cluster we found was in the more dorsal part of the anterior insula, which has been related to control processes such as switching, inhibition and conflict (Chang et al. 2012).

On the other hand, the two types of task conditions showed a clear pattern of lateralization. Whereas semantic cues engaged left hemisphere areas, spatial ones preactivated more bilateral regions with a general right hemisphere dominance. While the RSPL has been related to the relocation of top-down attention to relevant stimuli (Corbetta et al. 2008), its inferior part is closely involved in visuo-spatial perception (Constantinidis 2006; Husain and Nachev 2007) and orientation coding (Harris et al. 2008). The activation of this region, together with prominent visual ones, is coherent with the nature of the spatial task, in which participants had to tell the orientation of several lines superimposed in complex shapes. Although word perceptual analysis was also a requirement in the semantic task, which may be related to the increased connectivity of the LIFG with left fusiform regions, the type of fine visuospatial discriminations required in the spatial condition may explain the involvement of the RSPL in this condition. Moreover, the pattern of connectivity of this area during the cue period emphasizes the role of a dorsal occipito-parietal processing stream in preparation for upcoming demands of spatial perception (Husain and Nachev 2007; Goodale and Milner 1992).

Several theories propose the existence of common brain networks underlying preparation across categories. For instance, Dosenbach et al.'s (2008) cognitive control model posits the existence of two differentiated networks, one for initiation (frontoparietal) and a different one for the maintenance of task sets (cingulo-opercular). Other prominent theories, such as Duncan's (2010) Multiple Demand system, also support the implication of frontoparietal networks in flexible reorganization of cognitive states, such as those required in our task. Our results strongly suggest the presence of both general and task-specific preparatory processes for both categories in low-interference contexts. These are reflected in differential patterns of activation and connectivity for semantic and perceptual cues, which are coherent with later target-related activity in both cases.

Our results are coherent with previous literature on task preparation (see Sakai 2008) and, most importantly, they advance knowledge in the field showing specific task-related preactivations in a low-interference context. It could be argued, however, that our symbolic cues still required a certain memory load to be maintained during the cue-target interval. In addition, due to scanner equipment constraints the same fingers were used for both tasks, which could have induced some interference due to potential updates of response mappings (Meiran 2000). Indeed, achieving a complete lack of prospective memory load and interference in settings designed to study preparation is difficult, if not impossible. Preparing for something requires maintaining a set across time, and thus removing maintenance altogether would entail abolishing preparation. Thus, it is highly likely that the process of preparation, per se, is inextricably linked to prospective memory to a certain degree. The inclusion of a large target set in our design, however, minimized the role of working memory per se, in the sense of controlled manipulation of item information. Cue-target compounds could not be formed and thus cues could not trigger the anticipated imagination or manipulation of specific stimuli. Our results, obtained in a paradigm minimizing the influence of these factors, show that clear preparatory effects are nevertheless observed.

Conclusions

The current investigation represents a step forward in our understanding of selective preparatory processing in the brain. Our data are in line with predictive coding theories, which propose that the brain anticipates upcoming scenarios by creating a potential template of stimulation that is later on compared against the actual sensorial information (e.g., Friston 2003). Just like our brain represents the prediction of the perception of a face before its appearance (Summerfield et al. 2006), it also seems to recruit in advance areas needed for category-specific computations over stimuli whose specific content is unpredictable.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Apéndice 4

González-García, C., Arco, J. E., Palenciano, A. F., Ramírez, J., & Ruz, M. (2017). Encoding, preparation and implementation of novel complex verbal instructions. *NeuroImage*, 148, 264-273. http://dx.doi.org/10.1016/j.neuroimage.2017.01.037

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Encoding, preparation and implementation of novel complex verbal instructions

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ABSTRACT

Verbal instructions allow humans to acquire and implement complex novel rules in few seconds. A major question that remains elusive is how the brain represents this information prior to successful task execution. In this experiment, we studied the brain regions involved in representing categorical stimulus information during the encoding of novel instructions, their preparation and also their implementation, as well as the relation of the fidelity of these representations to observable behavior. To do so, we devised a novel instructions paradigm to delimitate these three stages. Using univariate and multivariate analyses of functional magnetic resonance data, our study revealed that the semantic content (faces or letters) of complex novel instructions can be decoded several seconds before the onset of a target, as soon as instructions are encoded. Crucially, the quality of the information represented in domain-general and category-selective regions correlated with subsequent behavioral performance. This suggests that the rapid transformation of novel instructions into coherent behavior is supported by control mechanisms that use available, relevant information about the current rule prior to its execution. In addition, our results highlight the relation between these control processes and others such as prospective memory and maintenance of future intentions.

Introduction

The ability to implement verbal instructions allows humans to translate novel complex rules into behavior in mere seconds. How does the brain deal with new information in such a fast and efficient way? According to theoretical models, the path from instructions to overt behavior can be decomposed in different stages of processing (Bunge, 2004; Sakai, 2008). Initially, the content of the instructions has to be *encoded* in the system, employing representations of semantic rules that link specific stimulus features to concrete behaviors (Crone et al., 2006; Sakai, 2008). Once the target context (stimuli) appears, instructions are *implemented* by performing the appropriate actions according to the instructed rules. But before that, *preparation* entails a task set configuration (Meiran, 1996; Rubinstein et al., 2001). This stage of processing, understood as the adjustment to relevant task rules in anticipation of target stimuli (Rogers and Monsell, 1995) is a key component of complex task execution (Brass and von Cramon, 2002), and it is thought to be a cognitive state separable from related ones, such as the mere maintenance of task demands (Cohen-Kdoshay and Meiran, 2009; Liefooghe et al., 2013, 2012; Muhle-Karbe et al., 2014). Crucially, the adequate configuration of cognitive resources achieved during the preparatory period enhances behavioral performance (Sakai, 2008).

Neuroimaging data suggest that task preparation relies on a frontoparietal network, which has been related to complex cognitive control operations (Duncan, 2010). More specifically, when switching between tasks the Inferior Frontal Junction (IFJ) updates the rule representation, whereas stimulus-response associations engage the intraparietal sulcus (IPS; Brass and von Cramon, 2004, 2002). De Baene and Brass (2014) proposed that the pre-supplementary motor area (pre-SMA) suppresses actions from previous tasks and enhances the appropriate response for the new stimulation. Previous studies also point to a dynamic interplay between the lateral prefrontal cortex (LPFC) and brain regions linked to category-specific processing (Sakai and Passingham, 2006, 2003). For instance, when participants prepare to perform semantic operations, task cues engage areas involved in effortful semantic processing, such as the left inferior frontal gyrus, prior to the target onset (e.g. González-García et al., 2016). Some other studies have also reported category-specific connectivity patterns in absence of changes in activity (Sakai, 2008). Although preparation

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seems to play even a more important role when we have to implement novel instructions (Norman and Shallice, 1986), the neural architecture supporting this ability remains unclear.

Novelty brings larger requirements of control processes given the lack of pre-existing task-rule representations (Cole et al., 2013). However, in most studies of task preparation and switching, participants alternate between a small number of highly practiced tasks, and thus task sets are formed in advance and later retrieved from memory (Cole et al., 2013). Preparatory processes, however, seem to fulfill somewhat different demands with new tasks. When we face a novel situation, retrieval of previous full task sets does not suffice. Rather, new ones have to be generated from scratch: representations (e.g. of visual cues) have to be created for each new trial, including sensory, semantic and goal-related ones. Recent research has coined the term of Rapid Instructed Task Learning (RITL) to refer to the "ability to rapidly restructure one's behavior into novel configurations from instructions" (Cole et al., 2013). To differentiate this type of learning from others, such as trial-and-error learning, most of the RITL research focuses on the first time a given task set is presented. This strategy uses several new instructions together with practiced ones, which allows the comparison between the retrieval of previously practiced sets and the actual formation of novel ones. Some studies (Cole et al., 2010; Ruge and Wolfensteller, 2010) have assessed the *implementation* of novel instructions, suggesting a novelty-related gradient within the LPFC in which there is an anterior-to-posterior shift of activation as task sets transition from novel to practiced. Regarding *preparation* for novel tasks, the frontoparietal network also seems to be involved. For instance, Hartstra et al. (2011) highlighted the involvement of IFJ and IPS during the presentation of single words that encoded instructions. They also revealed the involvement of the dorsal pre-motor and M1 areas, a result that they interpreted as a correlate of motor imagery and the creation of memory codes for the instructions. Using also isolated words, a later study extended these results, revealing that the inferior frontal sulcus underpins the representation of task sets by creating a link between the stimulus and the motor response (Hartstra et al., 2012). Despite this suggestive evidence, these studies did not explore how the semantic content of the instructions was represented during their encoding and preparation. This is a crucial aspect, since relevant information is needed to create an accurate task configuration prior to task execution, as shown in task-switching. However, it is still unknown how and where this relevant information is represented during preparatory stages to support the translation of novel verbal representations into implemented rules.

Studies assessing the representation of specific information during stages of processing suggest that multivariate rather than univariate analysis of functional magnetic resonance images (fMRI) is more suitable for this matter. For instance, using single words as instructions, Cole et al. (2011) showed that a classifier could generalize to novel tasks when trained on practiced tasks with DLPFC fMRI patterns. Likewise, a classification algorithm was able to decode task sets within this region while the instructions were on the screen. However, there is an implicit difficulty to decode relevant preparatory information in classic RITL paradigms. Since participants have to encode a new instruction on every trial, it is hard to disentangle the activity specific to preparatory processes from encoding of the new verbal content of the instructions (Brass and von Cramon, 2002; Rogers and Monsell, 1995).

We designed a paradigm to isolate preparation from instruction encoding and later implementation. For this, we pseudorandomly manipulated the duration of the interval between novel instructions and novel target grids, and had participants prepare the novel instructions in only half of the trials. Similar strategies have been used to isolate the preparation component associated to novel instructions (Demanet et al., 2016). In addition, we employed complex verbal instructions rather than drawings or isolated words as used in previous studies (Cohen-Kdoshay and Meiran, 2009; Liefooghe et al., 2013, 2012). Although instruction implementation can be achieved via non-linguistic channels, verbal information is the most powerful means to convey novel instructions (Cole et al., 2013). Previous strategies, such as presenting novel symbols or images linked to specific responses, promote concrete stimulus-response pairings and visual imagery, which reduce the scope of the observations. Also, the instructions employed in the current study contained abstract rules, which entail less concrete commands than specific instructions (e.g. "If you see two squares, press A") and a larger number of potential perception-action scenarios (e.g. "If you see two vowels, press A"). Our verbal instructions posed yet another form of complexity as they allowed the combination of multiple rules (e.g. "If you see two contiguous green vowels of the same size, press A"), which is not easily achievable through non-linguistic instructions or single words.

In addition, our experiment employed a task designed to alleviate frequent confounds of task novelty and difficulty. As mentioned before, previous studies employ instructions practiced in advance as a contrast to novel ones (Cole et al., 2016, 2011; Stocco et al., 2012). However, this translates into practiced tasks that are easier to implement, since the mere presentation of the instruction elicits the adequate response, retrieved from memory, which leads to faster responses and higher accuracy scores. In our study, in contrast, every trial started with a *novel* complex verbal instruction. A subsequent cue indicated whether a novel or a practiced target grid would appear and prompted participants either to prepare to implement the previous instruction or to retrieve a response from memory upon later target presentation (see Section Design and procedure). This manipulation balanced demands across tasks and equated performance indexes across novel and practiced sets. Also, a secondary benefit was the increase in the number of novel instructions, which increased the power of the design to differentiate the encoding of instructions referring to different stimulus categories.

In sum, the main aim in our study was to advance our knowledge about how the brain uses new complex information to perform novel tasks. To do so, we used complex, fully grammatical verbal instructions referring to either faces or letters to assess which areas contained category-specific information during the encoding, preparation and implementation of novel rules. We predicted that partially differentiated patterns of regions would be involved in encoding vs. preparing for a new instruction, and that these would include areas related to cognitive control. Similarly, we expected that the semantic content of instructions would be decodable since their encoding, but that more regions would get involved when participant had to explicitly prepare, reflecting a finer tuning to relevant task information. In addition, we hypothesized that the degree of decodability of activity patterns of different categories would have a relation with observable performance, which would stress the relevance of these representations for actual behavior.

Materials and methods

Participants

Twenty-two students from the University of Granada (7 males; mean age: 23; range: 19–31) took part in the experiment and received 20€ in exchange. To encourage high performance during the task, participants were informed that the five of them with the highest scores (in terms of accuracy and reaction times) would receive 5 additional €. All participants reported normal or corrected-to-normal vision and no history of neurological disorders, and signed a consent form approved by the local Ethics Committee.

Apparatus and stimuli

We created an initial pool of 210 different verbal instructions that referred to either face or letter-related features of grids of stimuli. Face

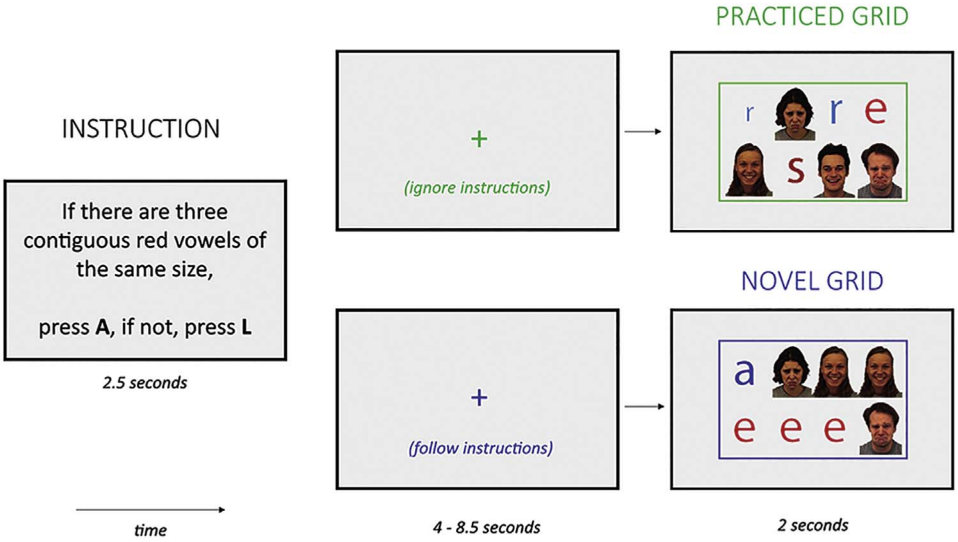

Fig. 1. Behavioral paradigm.

features were gender (male, female), emotion (happy, sad), size (large, small) amount (one, two, three or four faces) and contiguity (two, three or four contiguous faces). To create similar instructions for letter features, we equated face gender with type of letter (consonant, vowel) and face emotion with letter color (red, blue). Size, amount and contiguity were used in the same manner as in face-related instructions. Depending on the instruction, participants had to focus on one or several features of the same stimulus category. Instructions always used a conditional structure, such as "If there are three contiguous [e.g. female faces/red vowels] of the same size, press A, if not, press L". Two unique grids of 4 faces and 4 letters (one fulfilling the instruction and the other one not) were created for each of the 210 instructions. Grids were drawn from a pool of 8 faces (one happy male, one sad male, one happy female, one sad female; each in large and small sizes) and 8 letters (one blue consonant, one red consonant, one blue vowel, one red vowel; each in large and small sizes). To equate displays across categories, we created the equivalent of each grid for the opposite category, following the equivalences described above (e.g. gender [male, female]=type [consonant, vowel]).

A preliminary behavioral pilot study (*n*=14) detected that 17 instructions yielded consistently low accuracies (≤75%), and thus these were removed from the instruction pool together with their equivalent counterparts in the opposite category. The final pool contained 176 instructions (88 faces, 88 letters) equated in difficulty (see Supplementary Table 1).

For the fMRI experiment, a PC running E-Prime 2.0 projected the stimuli onto a screen located at the back of the scanner. A set of mirrors mounted on the head coil was used for participants to see the screen. During the whole experiment, they used the index fingers of their right and left hand to make speeded discrimination responses to target grids by pressing one of two buttons on a MRI-compatible button box.

Design and procedure

To create a baseline to compare against novel trials that was equated in behavioral difficulty (as assessed by speed and accuracy of responses), the day before scanning participants practiced a set of eight instructions (half referring to faces and the other half to letters; extracted randomly without replacement from the instructions pool) and their associated target grids. This practice session lasted ~20 min (8 presentations of each instruction) and was repeated until participants achieved ≥90% of accuracy. To ensure that participants had learnt the response to the eight grids, afterwards they were prompted to answer to the same grids, this time *without* seeing the associated instructions in advance. Therefore, by the end of the practice session participants had learned both grid-response and instruction-grid associations. This session also repeated until participants achieved ≥90% of accuracy, and lasted ~15 min (8 repetitions of each grid). If participants failed to complete the last phase after three repetitions, they had to repeat the complete learning session again (which happened to 3 of them). On average, participants practiced each instruction 20.6 times (SD=6.42), during approximately 43 min. Before the scanning session (which usually took place the day after the practice and never more than 9 days apart, with an average interval of 1.86 days), participants performed a ~5 min behavioral rehearsal session in which they again had to respond to the eight grids without their corresponding instruction. During the entire learning session, feedback was given after each trial to make participants aware of their performance and help them improve.

Scanning comprised a total of 160 trials. In each of these, regardless the type of trial, a novel instruction appeared. The color of the subsequent fixation cross (blue or green) signaled whether participants had to follow the instruction (80 trials) and thus prepare to implement it with a novel grid of stimuli or, alternatively, whether they had to ignore it (80 trials) and expect one of the eight practiced grids. For these practiced grids, participants had to respond based on the knowledge acquired during the learning session (see Fig. 1).

The associations between type of trial (novel, practiced), category and response options were counterbalanced across participants. The duration of the fixation cross indicating the type of trial, as well as inter-trial intervals, were jittered to allow the deconvolution of instruction- and grid-related signals. The pseudorandom duration of the preparation interval allowed the disambiguation of this stage from the encoding and implementation. Each trial comprised the following events (see Fig. 1): a 2.5 s instruction, a colored fixation cross (mean 6.25 s, range 4–8.5 s), a 2 s grid and an inter-trial interval displaying a black fixation cross (mean 6.25 s, range 4–8.5 s). On average, a trial lasted 10.750 s. The total fMRI task lasted 45 min approximately.

Data acquisition

Magnetic resonance images were acquired using a 3 T Siemens Trio scanner at the Mind, Brain and Behavior Research Center (CIMCYC) in Granada (Spain). Functional images were obtained with a one-shot T2*-weighted echo planar imaging (EPI) sequence (time until echo [TE]=23 milliseconds (ms), flip angle=70 degrees, repetition time [TR] =2.21 s). Forty descending sagittal slices with a thickness of 2.3 mm (mm; gap of 20%) covered the entire brain (voxel size of $3 \times 3 \times 3$ mm^3).

The event-related experiment was performed in a run consisting of 1240 volumes. In addition, we acquired a standard structural image of each participant using a high-resolution T1-weighted sequence (TR=1900 ms; TE=2.38 ms; 1×1 mm^2 in-plane resolution and 1 slice thickness).

We used SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) to preprocess and analyze the neuroimaging data. The first 4 volumes were discarded to allow for saturation of the signal. The images were then realigned and unwarped using a least-squares approach and a six-parameter (rigid body) spatial transformation to correct for motion artifacts. Then we used slice timing correction to account for differences in the time of slice acquisitions. Afterward images were normalized to the standard EPI template included in SPM8 and spatially smoothed using an 8 mm full-width at half-maximum isotropic Gaussian kernel. A 128 s high-pass filter was used to remove low-frequency artifacts.

Univariate analyses

Statistical analysis was performed with a General Linear Model (GLM) for each participant with corrections for serial autocorrelations using the AR(1) model. The model included regressors for Encoding (faces/letters instructions), Preparation (jitter of novel faces/letters task; jitter of practiced task), and Implementation (novel grid of faces/letters task; practiced grid faces/letters task). These regressors were convolved with the standard hemodynamic response function. Duration and onset vectors for the preparation interval were introduced into the GLM, whereas instructions and grids were modeled as events with zero duration. Trials with errors and missing responses were grouped together as separate events with an extended duration for the whole trial (encompassing instructions, fixation cross and grid). Contrasts of interest (i.e. Encoding vs. Baseline; Novel preparation vs. Practiced preparation; Novel implementation vs. Practiced implementation; Faces vs. Letters encoding; Faces vs. Letters novel preparation; Faces vs. Letters novel implementation) were obtained for each participant and then entered into a second-level analysis, where a *t*-test (t_o) was used to contrast conditions. To assess significance of each contrast at the population level, a non-parametric permutation-based approach was followed (Eklund et al., 2016), using the Statistical non-Parametric Mapping toolbox (SnPM13; http://warwick.ac.uk/snpm). On each permutation, the signs of the individual scores were randomly flipped and a new *t*-test was performed. This was repeated 5000 times, obtaining the true distribution of *t*-values, to which t_o was empirically comparable. Cluster-wise inference with a cluster-defining threshold of $p < 0.001$ was later used to find significant clusters (FWE corrected, $p < 0.05$) on the resulting map. It is worth noting that on this as well as on the analyses that follow, results were almost identical to those obtained using a parametric cluster-wise FWE correction approach (obtained from an initial uncorrected $p < 0.001$) as implemented in SPM12.

After the identification of areas involved in the encoding and preparation stages, we conducted a conjunction analysis (Nichols et al., 2005) to look for brain regions shared by the two stages. For conjunction analyses, we performed one-way ANOVAs using first-level contrast images of interest, which allowed us to define which clusters were significantly active both during encoding and preparation. Only conjunction clusters surviving a MS/CN test (Minimum Statistic compared to the Conjunction Null; Nichols et al., 2005) are reported.

Multivariate analyses

We employed multivariate pattern analysis (MVPA) to study brain regions sensitive to different stimulus categories (face vs. letter) during the encoding, preparation and implementation of novel instructions. This decoding was performed on the non-normalized and non-smoothed images. For each participant, we used a Least-Squares Separate model (LSS; Mumford et al., 2012; Turner et al., 2012) to reduce collinearity between the BOLD signal of consecutive events (Abdulrahman and Henson, 2016). Following this method, on each trial we fitted the standard hemodynamic response function to two regressors: (1) one of the events of the trial (e.g. novel grid of faces) and (2) the rest of events and trials. The output of this model was one beta image per event. To maximize the independence of training and test sets (Pereira et al., 2009), the total amount of betas obtained with the LSS model was split in 8 temporally distant chunks, each of which contained 5 betas per event of interest. For instance, for a given event (e.g. novel grid of faces), we grouped together the five betas closest in time (Turner et al., 2012). It is important to note that although these events were not always consecutive, since the different conditions were randomly interleaved, each chunk contained the trials closest in time. On average, each of these chunks comprised 340 s, being the average separation of train and test sets 510 s, and the distance between the two closest chunks 170 s.

To avoid biases in the selection of regions of interest (Kriegeskorte et al., 2009) we employed a searchlight approach (Kriegeskorte et al., 2006) across the whole brain. We used The Decoding Toolbox (Hebart et al., 2015) to create a spherical cluster of 4-voxel radius around a given voxel V_1, containing $C_{1 \ldots N}$ voxels. In order to cross-validate the performance of the decoder, accuracy was estimated following a leave-one-out scheme, with each chunk acting as test set once (Pereira et al., 2009). On each fold, a linear support vector machine (C=1) was trained to classify the patterns of each category in 7 of the 8 chunks (training set). Then, the algorithm's decoding accuracy was tested in the remaining chunk (test set). The averaged accuracy (see Results section) revealed the algorithm's ability to classify spatial patterns of each category in the cluster centered in V_1. This procedure was repeated for $V_{2 \ldots N}$ in each participant and for each event (encoding, novel preparation and novel implementation). The resulting accuracy maps for each participant and event were then normalized to a standard EPI image and smoothed with a 3-mm Gaussian kernel. The smoothed images were entered in a second-level analysis. Statistical correction was performed using the non-parametric approach described in the GLM section. The surviving clusters localized brain areas in which the algorithm's accuracy was above chance, that is, areas in which the spatial patterns for faces and letters were significantly different.

Correlations between decoding accuracies and behavioral indices

To test the behavioral relevance of the decoding results, we conducted a correlation analysis between individual behavioral indices (average reaction times [RTs] and accuracy on novel instruction trials) and decoding accuracies from significant clusters in the searchlight, using a permutation approach to correct for multiple comparisons (Groppe et al., 2011). For a given comparison between the behavioral index and a significant cluster across participants, we first calculated a correlation index, r_{observed}. We then shuffled participants' scores within one of the variables and performed the correlation test again. We carried out this step 10,000 times for each comparison, obtaining a null distribution of random r_N values with the null hypothesis that the two variables were not correlated (i.e. no relationship between the decoding accuracy of a given cluster and the behavioral index). To prove this hypothesis wrong, the $\text{r}_{\text{observed}}$ should be greater than the 95% of r_N. Only correlations with *p*-values smaller than 0.05 are reported.

In addition, to rule out the potential confound of RT-related variance in the hemodynamic response, a control analysis was performed. Here, we estimated the betas for decoding again, but regressing out the specific RT of the trial to which the event belonged. We then performed the decoding with the new betas and the correlation between the decoder accuracy and behavioral measures. This approach yielded significant correlations in the same ROIs revealed by the original analysis.

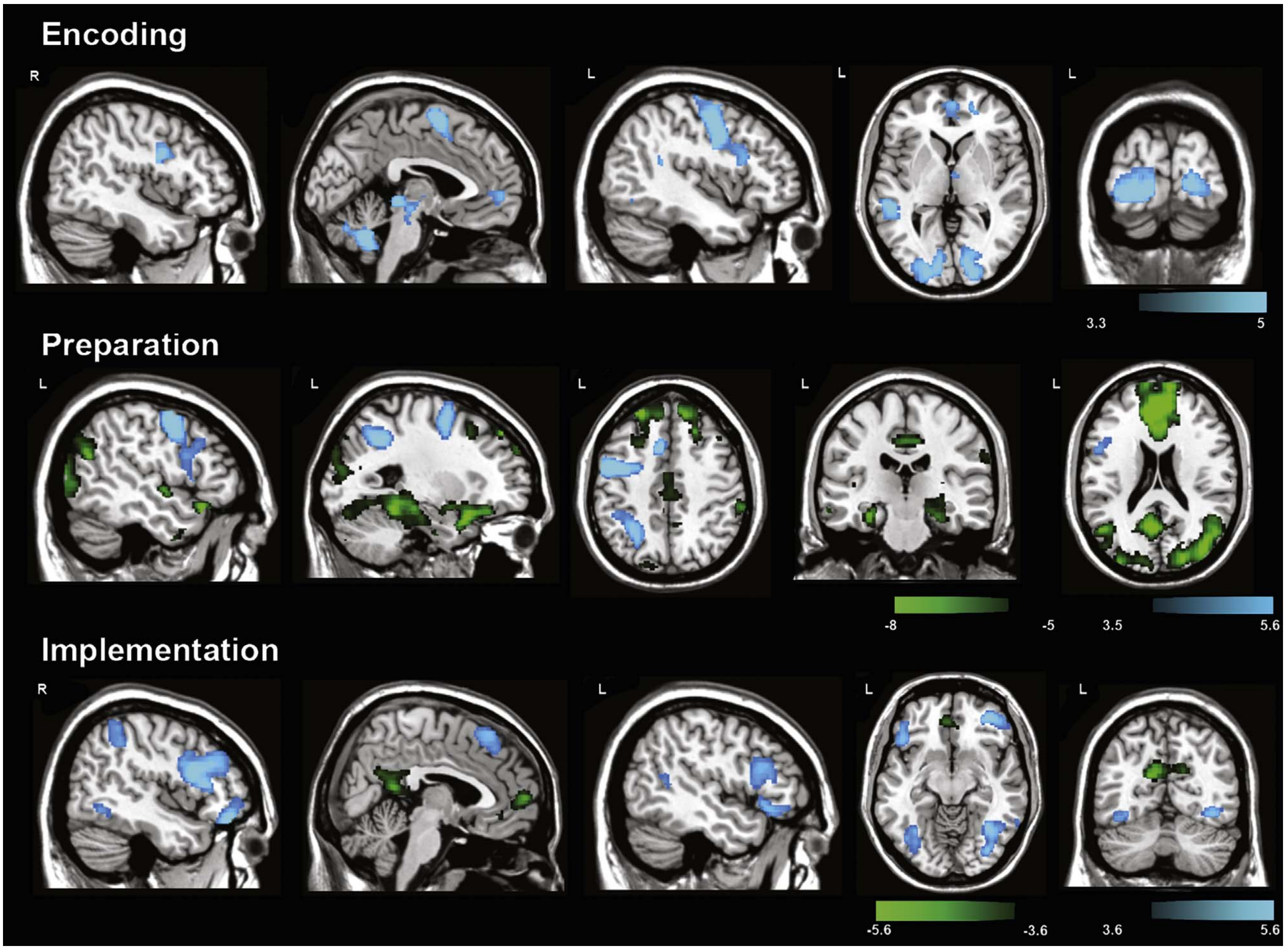

Fig. 2. Univariate results. GLM results for the encoding (novel instruction vs. baseline), preparation (follow instructions vs. ignore instructions) and implementation (novel grid vs. practiced grid). Blue colors indicate significant clusters for novel instructions, whereas green represents activity for the practiced condition. Scales reflect peaks of *t*-values.

Results

Behavioral

Differences between novel and practiced trials were not significant ($F < 1$ for accuracy scores and F=1.33, p=.26 for RTs). No significant differences were found between faces and letters for accuracy scores ($F < 1$), whereas there was a marginally significant effect for RTs (F=4.12, p=.06). These were nominally longer for faces (M=1109.27 ms; SEM=24.73 ms) than for letters (M=1067.42 ms; SEM=25.77 ms). Additionally, there were no significant interactions (all $ps > .1$).

Univariate

We first looked for activity across categories in novel trials, along the three temporal events of interest (encoding, preparation and implementation of instructions; see Fig. 1). The GLM during encoding (see Fig. 2) yielded significant clusters of activity (Instructions vs. baseline) in the ventral rostral prefrontal cortex (RPFC; x, y, z MNI coordinates of peak voxel: 2, 54, 0; k (cluster size)=91 voxels), superior medial frontal gyrus (MFG; 12, 45, 28; k=147), bilateral inferior frontal gyrus near the IFJ (42, −2, 24; k=138; −34, 14, 20; k=112), pre-SMA (−6, 0, 64; k=520), left premotor cortex (PMC; −48, −2, 36; k=519), left middle temporal gyrus (MTG; −54, −36, 2; k=480), right and left precuneus (28, −38, 22; k=27; −28, −54, 14, k=55), bilateral visual association areas (20, −94, −2; k=99; −16, −94, −8; k=123) and cerebellum (0, −58, −32; k=289).

During preparation, the contrast of novel against practiced trials showed a different pattern of activations. Preparing to perform a novel instruction engaged the left inferior frontal gyrus (−44, 22, 32; k=331), pre-SMA (−6, 2, 62; k=733), left PMC (−44, 0, 42; k=900) and the left inferior parietal lobe, near the IPS (−28, −52, 38; k=206). The opposite contrast revealed the strong involvement of default mode network (DMN) regions, including RPFC (0, 44, 22; k=3570), posterior cingulate cortex (PCC) (−4, −60, 22; k=3281), and left (−48, −62, 22; k=764) and right angular gyrus (60, −52, 34; k=830).

During the implementation of instructions, responses to novel grids (vs. practiced ones) revealed the activation of the ventrolateral prefrontal cortex bilaterally (48, 42, −16; k=74; −46, 28, −12; k=136), bilateral dorsolateral prefrontal cortex, including the IFJ, (50, 15, 16; k=643; −50, 20, 20; k=325), the right inferior parietal lobe (32, −52, 48; k=799), left MTG (−60, −52, 2; k=364) and the bilateral fusiform gyrus (34, −58, −10; k=210; −34, −62, −10; k=131). The opposite contrast yielded the activation of part of the DMN, namely, the RPFC (−2, 56, 6; k=536) and precuneus (−6, −48, 12; k=783).

However, no clusters survived the statistical threshold when contrasting faces vs. letters during encoding and preparation for novel trials. During implementation, only a cluster located in visual areas near BA18 (25, −92, −2; k=136) was more active for face than for letter grids.

Conjunction analysis

A one-way ANOVA with both the encoding and preparation regressors revealed a significant cluster involving the left inferior

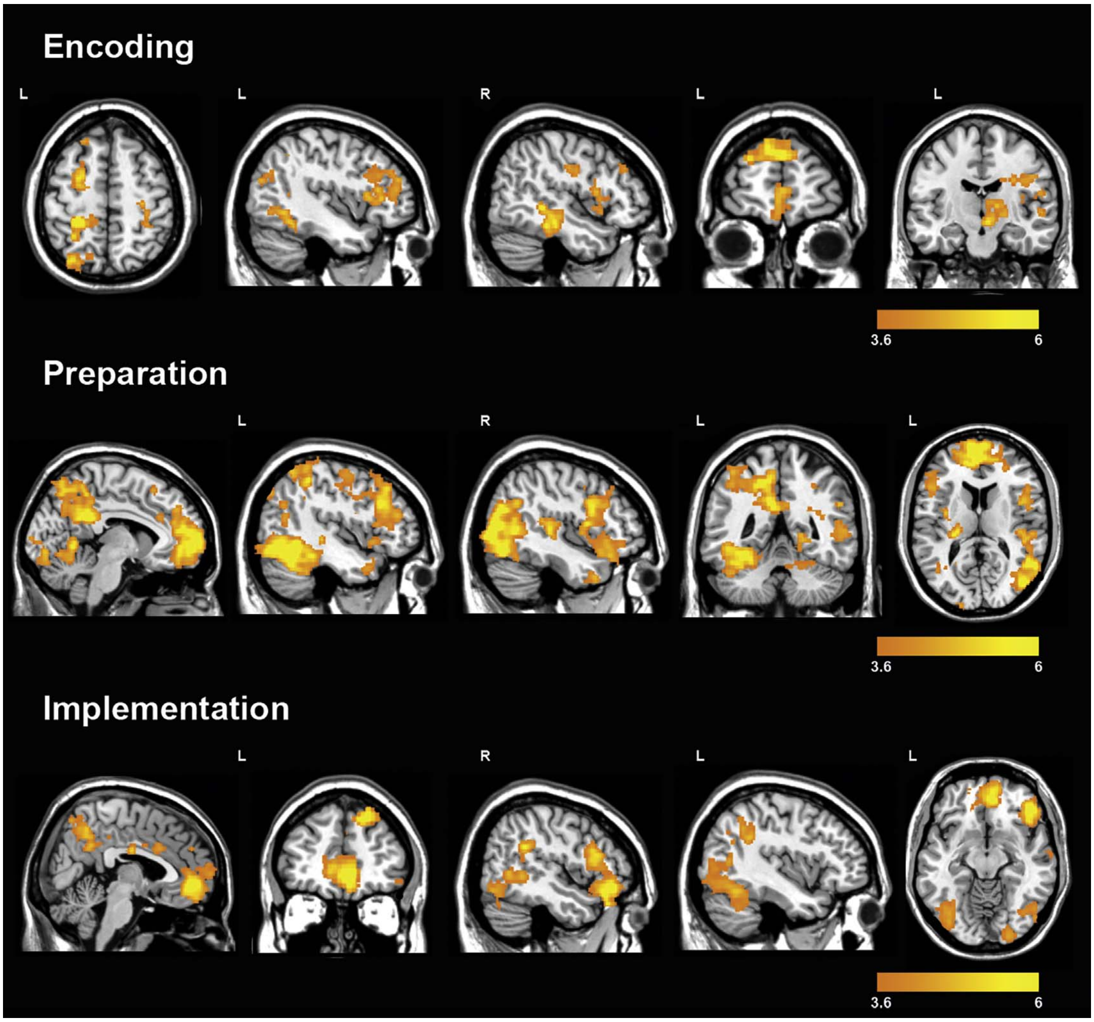

Fig. 3. Multivariate results. Differentiated spatial patterns for stimulus target categories (faces vs. letters) during encoding, preparation and implementation of novel instructions.

frontal gyrus (−42, 16, 24) and PMC (−40, −2, 44), and an additional cluster in the pre-SMA (−4, 2, 64). These results suggest that these three regions were active during both encoding and preparation of novel instructions. According to this results, the IPS seems to be the only region active exclusively during the preparation stage. To confirm the absence of IPS involvement during instruction encoding, we performed a region of interest-based comparison of instructions vs. baseline for the IPS cluster drawn from the preparation contrast. This did not yield significant results even after lowering the threshold at uncorrected $p < .1$.

Multivariate

While the instructions were on the screen, several regions showed differentiated spatial patterns of activation for encoding letter vs. face-related verbal instructions (see Fig. 3), including the ventral RPFC (−2, 58, −6; *k*=711; 54%), superior MFG (−2, 56, 28; *k*=546; 53.5%), left superior frontal gyrus (−24, 0, 56; *k*=135; 53.2%), left (−28, 32, 32; *k*=720; 54.1%) and right inferior frontal gyrus (48, 8, 12; *k*=41; 53%), right thalamus (16, −16, 6; *k*=352; 54%), left postcentral gyrus (−32, −38, 58; *k*=174; 53.3%), left superior parietal gyrus (−26, −42, 54; *k*=477; 54%), left angular gyrus (−36, −66, 26; *k*=65; 53.4%), left fusiform gyrus (−46, −58, −6; *k*=101; 53.4%), right lingual gyrus (18, −82, −10; *k*=388; 54.1%) and right cerebellum (28, −64, −42; *k*=567; 53.4%).

Preparation to perform either a letter or a face novel task elicited separable spatial patterns of activity in the ventral RPFC (2, 58, −2; *k*=1244; 57.3%), a large cluster in the left dorsolateral prefrontal cortex including the IFJ (−30, 26, 50; *k*=2754; 56.2%), right inferior frontal gyrus (48, 10, 24; *k*=2191; 56%), left parahippocampal gyrus (−24, −14, −16; *k*=639; 55.5%), precuneus (−6, −44, 26; *k*=2953; 56.5%), right angular gyrus (52, −58, 14; *k*=351; 55.3%), left fusiform gyrus (−34, −52, −18; *k*=936; 57.5%), and right (46, −76, 8; *k*=1315; 57.1%) and left (−46, −78, −12; *k*=560; 56%) lateral occipital complex (LOC; see Fig. 3).

A conjunction analysis (Nichols et al., 2005) of the encoding and preparation stages revealed that the RPFC (0, 60, −2), left dorsolateral prefrontal cortex (−44, 24, 32), right inferior frontal (48, 8, 18), left superior parietal (−34, −76, 50) and left fusiform gyri (−50, −56, 10) represented relevant information in both stages of instructions processing.

Last, the stimulus category of novel tasks during implementation was encoded in the RPFC (6, 50, −4; *k*=545; 59%), superior frontal gyrus (18, 48, 52, *k*=343; 52.69%), right ventrolateral (42, 30, −16; *k*=261; 58.4%) and left dorsolateral prefrontal cortex (−46, 28, 24; *k*=196; 55.5%), anterior cingulate cortex (−8, 24, 24; *k*=186; 55.8%), right MTG (64, −10, −22, *k*=193; 55.5%), precuneus (−4, −64, 44; *k*=1885; 52.88%) and bilateral inferior parietal lobe (36, −50, 28; *k*=169; 55%; and −32, −56, 36; *k*=407; 56.4%, respectively).

Correlations between decoding accuracies and behavioral indices

We introduced the decoding accuracies of the peaks within significant clusters of the MVPA results and the average RTs and accuracy

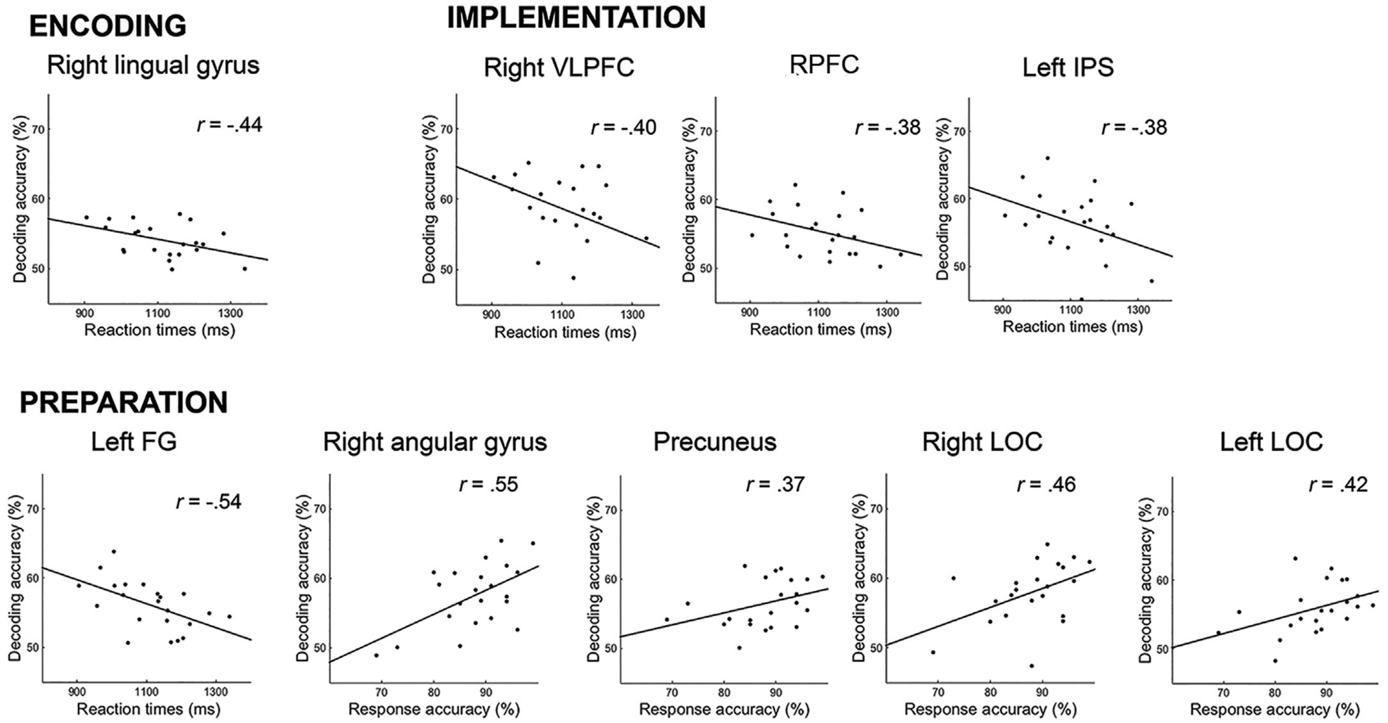

Fig. 4. Correlations between decoding and behavior. Scatter plots of significant correlations (corrected at $p < .05$) between decoding accuracies and behavioral indices of novel tasks. Initials stand for Fusiform Gyrus (FG), lateral occipital complex (LOC), ventrolateral prefrontal cortex (VPFC), RPFC (rostral prefrontal cortex) and intraparietal sulcus (IPS).

scores per participant into a correlation analyses. After correcting for multiple comparisons (see Section Correlations between decoding accuracies and behavior indices), this analysis revealed a significant negative correlation between the decoding of the instruction category (faces vs. letters) in the right lingual gyrus during the encoding period and RT (*r*=−.44, *p*=.02; see Fig. 4). During preparation for novel trials, RT negatively correlated with the decoding of the category in the left fusiform gyrus (*r*=−.54, *p*=.005). Moreover, during this stage response accuracy positively correlated with the decoding of the category in the precuneus (*r*=.37, *p*=.04), right angular gyrus (*r*=.55, *p*=.005), and right (*r*=.46 *p*=.02) and left (*r*=.42 *p*=.02) LOC. Regarding the implementation stage, RT negatively correlated with the decoding accuracy in the RPFC (*r*=−.38, *p*=.04), the right ventrolateral prefrontal cortex (*r*=−.40, *p*=.03) and the left IPS (*r*=−.38, *p*=.04).

Discussion

In the present study, we assessed how the brain encodes the content of information conveyed by complex novel instructions. Using multivariate analysis, we have shown for the first time that the content of complex verbal instructions can be decoded during the encoding, preparation and implementation phases of novel tasks. Moreover, the decodability of category-specific information in high-order and selective processing brain regions during these stages has an impact on subsequent behavior.

As expected, our paradigm equated demands between novel and practiced tasks, as shown by behavioral measures, ruling out difficulty confounds. Moreover, performance was similar for faces and letters trials. Although we found a close to significance trend in RTs, a control analysis (see Section Correlations between decoding accuracies and behavior indices) confirmed that our decoding results, as well as the correlations of decoding accuracies with behavioral variables, were not affected by this speed of responses. The design of the paradigm also facilitated the separation of encoding, preparation and implementation stages. During the presentation of the verbal instructions on the screen, participants were asked to encode their content, which included the perceptual category of the stimuli (faces vs. letters) that the instructions referred to. Crucially, at this stage, they did not know whether they would be required to later implement these instructions, which discouraged explicit preparation during this first, encoding period. The color of the subsequent fixation point carried this information, and in half of the trials participants had to prepare to perform the instruction just encoded, which would be implemented once the target grid appeared. On the other half of the trials, the color of the fixation point indicated that a practiced grid would appear and prompted participants to disregard the new rule and answer based on what they had learned during the practice session. This manipulation allowed us to study a component of explicit preparation, as well as differentiate it from the encoding of the verbal content, as discussed below. It is important to highlight that these instructions were complex abstract sentences, fully grammatical, rather than isolated words or pictures. Also, they prepared to respond to complex and variable target grids rather than to isolated stimuli. Hence, the results observed are hard to explain in terms of perceptual imagery.

Univariate results showed that encoding novel instructions engaged brain regions associated to instructed behavior, such as the IFJ, the pre-SMA and the PMC, which were also active during preparation. This suggests that even when participants do not know if they will be required to implement an instruction, its mere reading activates a new task set. This could reflect an automatic encoding of verbal instructions (Liefooghe et al., 2012) or, alternatively, a planned strategy of participants, by which they would willingly encode the new task set and decide whether to prepare or discard it later on. Either way, our results show larger involvement of the IPS during the preparatory stage compared to the encoding of instructions. This is in line with experimental models of executive control that propose that the activation of action-related codes occurs after completion of the task goal update (Rubinstein et al., 2001) and with empirical data that show the transmission of top-down representations from prefrontal to parietal neurons (Crowe et al., 2013, but see Bode and Haynes, 2009, for an alternative claim). Despite other regions related to action processing were active during the encoding phase, these have been previously related to the suppression of previous task sets actions and the establishment of appropriate motor codes (De Baene and Brass, 2014; Hikosaka and Isoda, 2010). In general, our univariate results support the idea that instructions can foster the creation of S-R associations in a rather automatic manner (Liefooghe et al., 2012), but still a greater degree of preparation is needed for them to elicit action codes (Liefooghe et al., 2013; Meiran et al., 2012; Wenke et al., 2009). Similarly, Liefooghe et al. (2013) suggest that verbal instructions can be encoded in a declarative or a procedural format. According to these authors, only when the instruction has to be enacted in the future the declarative information is translated into an "action-based format". Wenke et al. (2009) propose that this translation entails the activation and binding of relevant features, which would take place during preparatory stages in our study. Likewise, Muhle-Karbe et al. (2014) used transcranial magnetic stimulation to show that the late disruption of IPS activity hindered the translation of abstract rules into specific motor commands. Hence, our results highlight the involvement of the IPS in binding stimulus and action features (Hartstra et al., 2012) and suggest a key role of this region while preparing to perform novel tasks. Last, during implementation, even with equated behavioral performance between novel and practiced trials, we found increased activation in lateral prefrontal and parietal cortices linked to novel targets. This result stresses the relevance of these regions in novelty processing, and not merely in more difficult contexts.

Univariate analyses, however, were not sensitive to the content of novel instructions. This lack of univariate sensitivity prior to target appearance is not uncommon in the literature (Sakai, 2008). Multivariate analyses, on the other hand, were more sensitive. During the encoding stage, content information could be decoded from high-order areas such as the IFJ, angular gyrus and the RPFC, as well as regions related to letter and word processing, such as the lingual (Borowsky et al., 2007; Leshikar et al., 2012; Vinckier et al., 2007) and fusiform gyri (Harris et al., 2016; McCandliss et al., 2003; Roberts et al., 2013). Our results show that these regions, which previous results link to lexical-semantic processing of sentences (e.g. Ye et al., 2011), are involved in encoding the semantic content of novel instructions. Crucially, prior to target onset, the content of instructions could also be decoded from category-selective regions, such as the fusiform gyrus or lateral occipital complex, key hubs for object processing (Eger et al., 2008a, 2008b; Grill-Spector et al., 2001). These results are coherent with the idea that prospective cognitive control processes engage not only higher-order, frontal areas but also specific processing regions involved in forthcoming stimulation (González-García et al., 2016; Sakai and Passingham, 2003). Previous studies that also reported results on the same line during preparatory stages (Muhle-Karbe et al., 2016) employed images of drawings to instruct new rules, which most likely engaged subsequent mental imagery retrieval of specific perceptual material. Our design, in contrast, employed complex verbal instructions composed of words and with no pictures, and therefore the information represented in perceptual regions had to be activated by the semantic content of the instructions *per se*, rather than the perceptual processing of images. Last, preparation also engaged a set of regions that has been previously related to episodic retrieval and recombination of related past events, such as the RPFC, PCC, parahippocampal cortex and angular gyrus. Interestingly, some of these regions are part of the DMN. We will return to this point later on the Discussion.

An important finding of the present study is the observed link between the quality of the representations during different stages of novel instruction processing and behavior. This relationship between decoding efficiency in novel tasks and behavior has been reported in previous studies. For instance, Etzel et al. (2015) revealed an increase in the quality of rule representations in the brain when participants received monetary incentives. Similarly, Cole et al. (2016) showed that task representations within the DLPFC are behaviorally relevant in the *implementation* of novel tasks, since the accuracy of the decoder increased during correct in comparison with error trials. Results from the current experiment show that the discriminability of the perceptual categories referred to during the *encoding* and *preparation* of novel instructions also influence the efficiency of posterior behavioral responses. Interestingly, while during encoding and preparation there were significant correlations between behavior and decoding in some brain regions related to selective processing of objects, such as the lingual gyrus, fusiform gyrus and lateral occipital complex, during implementation these correlations were found in frontoparietal areas involved in cognitive control. Previous studies suggest that the IFJ drives category-specific regions involved in feature-based attention (Baldauf and Desimone, 2014). In this line, we hypothesize that before target onset, the updating of the task rule in the IFJ (Brass and von Cramon, 2004, 2002, Hartstra et al., 2012, 2011), replicated by our univariate analysis, is followed by the tuning of object processing areas such as the fusiform gyrus and the lateral occipital complex, as well as areas involved in episodic retrieval and recombination of past events (Lundstrom et al., 2005; Wagner et al., 2005). This tuning would enhance the integration of patterns of similar instructions and separation of irrelevant ones, which could explain the reported impact on subsequent behavior. During the implementation of the rule, this simultaneous pattern integration and separation would have the largest effect on cognitive control areas (Schlichting and Preston, 2015). Interestingly, decoding accuracy correlated with RT in some areas and with response accuracy in other areas, but not with both indexes. It is also noticeable that correlations with response accuracy were only found during preparation, whereas significant correlations with RT were present during the three phases. This set of results is however puzzling as previous literature did not led us to predict such differences, which would be interesting to explore in future studies.

Our multivariate results are coherent with the existence of a compositional mechanism underlying the ability to follow novel instructions to implement new tasks (Cole et al., 2013). This notion resonates with the *constructive episodic simulation hypothesis*, proposed in the field of prospective memory. This hypothesis predicts that the simulation of novel future events relies on a flexible recombination of small details of past events (Madore et al., 2014; Schacter and Addis, 2009; Szpunar et al., 2014), which is in line with the idea that instructed learning takes advantage of working memory resources to support "rapid updating, composionality, and combinatorics of the representations within the task sets" (Cole et al., 2013). The recombination of past events recruits different brain areas, including not only the prefrontal cortex, but also the RPFC, lateral temporal and temporopolar cortex, hippocampus, parahippocampal cortex, lateral parietal and PCC (Schacter and Addis, 2009). Some of these areas have a direct relation with behavior during constructive simulation of novel future events, suggesting their important role in our task and paradigms alike. Accordingly, some authors have proposed that rule and motor representations of novel instructions might entail mental simulation (Brass et al., 2009). Similar ideas have been suggested in the study of goal setting and intentions. Locke and Latham (2002) proposed that, when confronted with new stimulation, people retrieve a repertoire of skills used in similar contexts and apply them to attain a novel goal. Moreover, Lau et al. (2004) revealed that attending to the intention to perform a motor action involved brain regions closely related to novel instruction processing, such as the pre-SMA and the IPS. Several prospective memory studies assessing the correlates of future intentions have shown the involvement of brain areas recruited by our task, mainly the ventral RPFC (Gilbert, 2011; Landsiedel and Gilbert, 2015; Momennejad and Haynes, 2013, 2012). A related striking finding of the current dataset is the encoding of semantic information in DMN regions. These results hardly reflect mind wandering, since participants had to actively retrieve the response to the given target, or some sort of processing of social information, since the required responses were based on perceptual rather than social features. Although the role of these regions in task setting is not clear, one possibility is that these areas are involved in the representation of the semantic content of internal speech and conscious thought (Huth et al., 2016). Accordingly, previous studies have highlighted the involvement of the DMN when large changes of the cognitive context take place (Crittenden et al., 2015), which potentially require prospective memory and active intentions. Also demanding prospective memory is the coding of task goals, which has been related to the frontal node of the DMN (Haynes et al., 2007) as well. Our results thus suggest that novel instruction processing is supported by some of these processes (such as internal speech, major revisions of cognitive context, recombination of past events, simulations of future events, encoding of intentions and attention to these). More research is needed to delimit the specific role of each of these processes in the implementation of instructions.

Conclusions

In sum, our results reveal that category-specific information of complex verbal sentences instructing novel tasks can be decoded from several brain regions. Moreover, we show for the first time that this information can be decoded starting from the encoding of verbal information in perceptual and semantic-related brain areas. Future research should address how the specific neural representation of the content of instructions varies across this large set of areas during different stages, as well as the associated pattern of connectivity. Moreover, future studies should aim at assessing different aspects of instructions, such as the level of compositionality of rules, abstraction, and relationships between concepts. This would provide useful insight about how specific semantic information is encoded in the brain (Huth et al., 2016). A further important issue to be resolved is how different cognitive control components, namely the maintenance of an overall task-set and adaptive task sets initiated on each trial, interact when we follow complex verbal instructions.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuroimage.2017.01.037.

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