Departamento de Psicología Experimental

Modulación y actualización dinámica del valor asignado a las relaciones entre los estímulos como forma de adaptación al medio. Un estudio del cerebro y la conducta

Tesis doctoral presentada por

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para optar al grado de Doctor en Psicología.

Dirigida por el Catedrático

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Sevilla, 2018

Este trabajo se lo dedico a mi familia

y a todas las personas que, en algún momento,

me han ayudado a crecer y mejorar en mi carrera profesional.

AGRADECIMIENTOS

Aprovecho este espacio para dar las gracias en primer lugar a Carlos, mi director de Tesis, por todo lo que me ha ayudado, enseñado, corregido y aportado durante los años que llevo trabajando a su lado.

Con no menos ímpetu, doy las gracias a todos los sujetos experimentales que, de manera voluntaria y desinteresada, decidieron colaborar como "donantes de ondas" en los estudios que han servido para publicar los artículos sobre los que versa la presente Tesis Doctoral.

Muchas gracias también a los miembros del Tribunal de mi Tesis por el tiempo y el esfuerzo que han dedicado a entender y valorar el trabajo que les presento.

Por último, dar mi agradecimiento a la Facultad de Psicología y a la Universidad de Sevilla por permitir que alumnos como yo sigan teniendo una formación amplia y de calidad.

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- Resumen

El ser humano se encuentra inmerso en un entorno plagado de estímulos que su cerebro percibe y procesa de forma constante. Gracias a este procesamiento se busca emitir las respuestas o los comportamientos más adecuados en cada momento y lugar. El resultado de dichos comportamientos es reevaluado continuamente con el fin de ir modificando la conducta para adaptarla al medio. En suma, nuestro cerebro contaría con un mecanismo que le permite (i) analizar el medio; (ii) filtrar y almacenar los conocimientos y experiencias importantes; (iii) utilizar esta información para predecir los eventos futuros; y (iv) emitir las respuestas más adaptativas ante cada situación. A nivel experimental, hablaríamos de un ciclo cognitivo que se repite constantemente, y en el que se transfiere la información (o la experiencia) de cada ensayo al ensayo siguiente, con el objetivo de adaptar las respuestas a los requerimientos de cada tarea (Fuster, 2004; Friston, 2010).

Partiendo de las ideas previas, el presente trabajo tratará de analizar cuáles son algunas de las bases neurales que forman parte de este mecanismo cognitivo. A través de la presentación de una tarea experimental conocida como Paradigma de las Claves Centrales de Posner (Posner, 1980), y mediante el uso de la electroencefalografía, se intentará generar y estudiar el ciclo de Potenciales Evocados que tiene lugar a la hora de (i) generar hipótesis, inducidas por claves ambientales, sobre ciertas características de los próximos eventos; (ii) percibir los nuevos eventos y emitir respuestas acordes; y (iii) confirmar o rechazar las hipótesis, con lo que se refuerza o se reevalúa la credibilidad de las claves como predictoras del próximo evento.

- Introducción

Desde el nacimiento, nuestro organismo se descubre inmerso en un mundo lleno de relaciones inciertas y cambiantes entre los estímulos que percibimos. Dentro de este mar de estímulos que percibir y procesar, el conocido como "Sistema Atencional" sería el encargado de lidiar con la incertidumbre y orientar nuestros recursos sensoriales de modo que podamos generar respuestas adaptativas en cada momento. Más concretamente, la atención selectiva sería la que nos permite procesar la información relevante y suprimir la irrelevante (Hillyard y col., 1973), incrementando nuestra capacidad perceptiva hacia ciertas localizaciones o estímulos (Hawkins y col., 1990). De forma similar, nuestro cerebro debe seleccionar las acciones más adaptativas en cada momento en base a los estímulos percibidos y la experiencia previa. En este contexto aparecería el concepto de "Atención Motora" (Goldberg y col., 1987; Verguts y col., 2009), introducido para indicar el proceso a través del cual los sujetos preparan determinados programas motores (omitiendo otros), del mismo modo que se preparan para percibir ciertos estímulos e ignorar otros.

Existen actualmente diferentes aproximaciones teóricas que tratan de arrojar luz sobre este proceso. Por un lado, se ha planteado el término "Ciclo de percepción-acción" (Fuster, 2004) para denominar este proceso de adaptación permanente al ambiente; nuestro cerebro estaría llevando a cabo una evaluación continua de las consecuencias de las acciones emitidas con el objetivo de ajustar al máximo el comportamiento a las demandas del ambiente (al mismo tiempo estaría actuando sobre el ambiente para hacerlo menos incierto). Desde otro punto de vista, se habla de una adaptación dinámica en base al cálculo de probabilidades (Knill y Pouget, 2004; Bruce y Tsotsos, 2009; Reynolds y

Heeger, 2009; Friston 2010; Feldman y Friston, 2010). Se trata de una aproximación matemática que considera que los sujetos están continuamente calculando la probabilidad de ocurrencia de las diferentes relaciones entre eventos; los estímulos considerados como clave (S1) nos ayudarían a predecir la ocurrencia de eventos futuros (S2), de modo que, en función de la confirmación o el rechazo de las predicciones, el sujeto iría modificando el peso probabilístico asignado a las diferentes relaciones (P (S2/S1)). En resumen, este tipo de modelo propone un cerebro capaz de crear una representación del mundo basada en la información percibida y la computación continua de las probabilidades entre los eventos.

> *Atención*

La idea de 'prestar atención' refiere al hecho de focalizar voluntariamente nuestra consciencia en algo concreto, descartando el resto de información que nos llega en ese momento. En este sentido, cabe destacar la distinción entre 'atención endógena' (guiada voluntariamente por metas y a la cual se refiere este trabajo) y 'atención exógena' (guiada por estímulo externos de forma automática o pasiva) (Corbetta y col., 2008). El proceso de 'prestar atención' lo llevan a cabo diversos sistemas neuronales que tratan de procesar el flujo constante de información sensorial percibida por el cerebro, de forma que se procesen los estímulos relevantes y, como consecuencia, se generen las respuestas apropiadas (Bench y col., 1993; Desimone y Duncan, 1995). El funcionamiento del mecanismo a través del cual trabaja el sistema atencional requiere un esfuerzo neurocognitivo tan relevante como el de la memoria o el aprendizaje. Sin embargo, la atención ha sido uno de los últimos procesos cerebrales en ser considerado como 'función cerebral superior'.

El interés científico que existe actualmente por comprender el funcionamiento del sistema atencional, viene justificado, entre otros motivos, por la gran cantidad de trastornos neurológicos que conllevan déficits atencionales (traumatismo craneoencefálico, Trastorno por Déficit de Atención e Hiperactividad (TDAH), epilepsia, demencia subcortical, SIDA, etc.). Además, el estudio de la atención en casos de pacientes psiquiátricos que padecían síntomas de esquizofrenia o depresión ha llevado incluso a plantear que puede haber un trastorno del sistema atencional detrás de estos cuadros (o por lo menos que los problemas atencionales son un síntoma nuclear de estos trastornos). De este modo, un mal funcionamiento atencional puede desembocar en un mal procesamiento de la información del entorno, que afectaría finalmente a las relaciones interpersonales y generaría un situación de estrés proclive al desarrollo de síntomas esquizofrénicos (Posner y Petersen, 1990; Cornblatt y col., 1992).

La atención puede ser definida como un mecanismo neuronal que focaliza y regula la entrada y el procesamiento de estímulos en el cerebro, permitiendo que ciertos estímulos se procesen con mayor o menor intensidad. Este mecanismo se va perfeccionando a lo largo del desarrollo, de forma que la persona va ganando precisión en procesos como la orientación, la exploración, la concentración, la vigilancia, la focalización, etc. (Mesulam, 1985). A nivel neural, la atención estaría compuesta por sistemas perceptivos, motores, límbicos y motivacionales; por lo que su neuroanatomía comprendería, entre otras, el sistema reticular activador, el tálamo, los ganglios basales, el cíngulo anterior, el córtex parietal posterior y el córtex prefrontal (Mesulam, 1991; Colby, 1991) (Figura 1). Además, cada hemisferio estaría funcionalmente especializado. El hemisferio izquierdo se ocuparía únicamente del control unilateral a su lado

contralateral, mientras que el derecho ejercería un control bilateral y se encargaría de mantener en funcionamiento el sistema de 'arousal', y de regular la atención selectiva (Cooley y col., 1990; Posner y Driver, 1992).

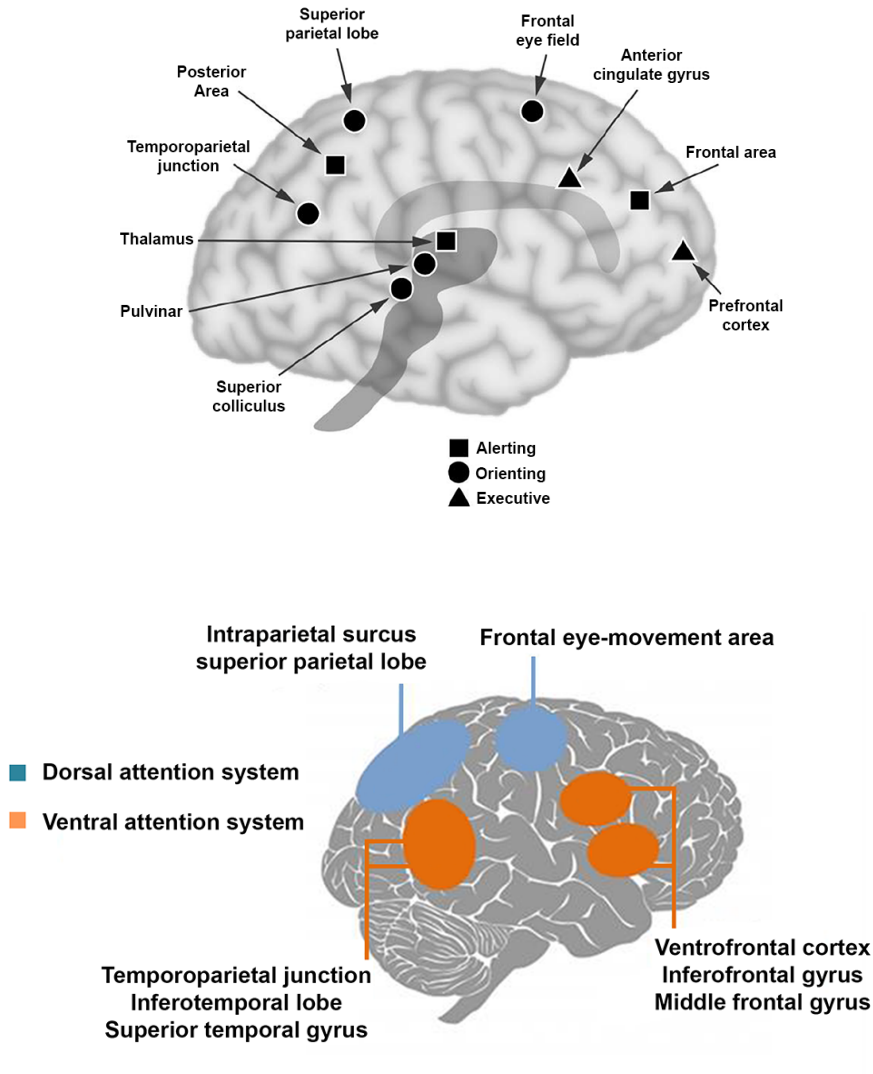

Figura 1. Áreas cerebrales implicadas en el funcionamiento de la atención (Corbetta y Shulman, 2002; Posner y Rothbart, 2007).

La atención visual sería una de las modalidades mejor estudiadas hasta el momento. Otras modalidades, como la atención somatosensorial o la auditiva,

funcionarían, en parte, a través de los mismos circuitos cerebrales que la visual. El funcionamiento de la atención implicaría la activación de una amplia red neuronal. Las conexiones entre el núcleo caudado, la sustancia negra, el colículo superior y el tálamo formarían el circuito básico subcortical (Hillyard 1985; Pardo y col., 1991).

A nivel funcional, hasta la fecha se han propuesto diversos modelos neurocognitivos en base a los cuales la atención puede ser dividida en varios tipos (Posner y Petersen, 1990; Cooley y col., 1990; Posner y Dehaene, 1991; Stuss, 1995). El estado de alerta o 'arousal' correspondería al nivel de conciencia determinado a través de registro neuroeléctrico. El 'span' atencional o amplitud de la atención se mediría en base al número de estímulos que una persona es capaz de repetir inmediatamente después de que se le presenten (dígitos, sonidos, etc.). La 'atención selectiva o focal' se implementaría a través del córtex parietal posterior y puede concretarse como la utilizada en tareas de búsqueda visual. La 'atención de desplazamiento' entre hemicampos visuales sería la que permite enfocar y desenfocar la atención a través de diferentes áreas del campo visual, evaluándose mediante el Paradigma de las Claves Centrales de Posner cuando el control es endógeno, y a través del Paradigma de Claves Periféricas cuando es exógeno (Posner y col., 1980; Corbetta y col., 2008). La 'atención serial' se activaría a la hora de realizar tareas de búsqueda de estímulos posicionados junto a distractores. La 'atención dividida o dual' sería la que permite realizar dos o más tarea al mismo tiempo. La 'atención de preparación' refiere al proceso atencional necesario para llevar a cabo una tarea cognitiva, escogiendo la información y las respuestas más adecuadas. La 'atención sostenida' permitiría mantener a la persona en estado de alerta o vigilancia de forma voluntaria y durante un tiempo prolongado (especialmente alterada en los casos de TDAH). Por último, la 'inhibición' se emplea cuando la tarea requiere descartar las respuestas

automáticas o naturales y emitir respuestas con un mayor nivel de procesamiento (por ejemplo en la prueba de Stroop).

En suma, el fenómeno de la atención conlleva una complejidad funcional y neuroanatómica tan variada que impide etiquetarlo bajo un conjunto definido de áreas o procesos neurales (Van Zomeren y col., 1994).

> *Teoría atencional de Posner*

A la hora de realizar estudios relacionados con la atención, una de las ideas que hay que tener presente es que se trata de un concepto que puede tener significados diferentes dependiendo del punto de vista desde el que se analice. Por ejemplo, podemos hablar de la atención como un proceso involuntario (algo llama nuestra atención) o voluntario (prestamos atención a algo).

Uno de los principales objetivos de los estudios científicos que se han llevado a cabo hasta ahora sobre la atención ha sido el de definir qué es la atención y cuáles son los procesos subyacentes que la controlan y definen. Hasta ahora, las diferentes teorías se han caracterizado por hablar de 'variedades atencionales'. Por ejemplo, algunos autores distinguen entre procesos selectivos, intensivos, de alerta y de mantenimiento (Parasuraman y Davies, 1984); otros entre atención, expectativa e intención (Van der Heijden, 1992); y algunos autores, como LaBerge (1995), hablan de distintas manifestaciones de la atención (selección, preparación y mantenimiento).

Dentro de este panorama tan diverso de conceptos relacionados con el fenómeno atencional, el Psicólogo Michael I. Posner y sus colaboradores propusieron una teoría integradora. Esta teoría planteó que existen diversos sistemas atencionales, relacionados entre sí, que son responsables de las diferentes manifestaciones planteadas hasta el momento. De este modo, la atención se entendería como un sistema modular compuesto por tres redes: (i) la Red Atencional Posterior (relacionada con la orientación a los estímulos), (ii) la Red de Vigilancia o Alerta y (iii) la Red Anterior o de Control Ejecutivo. Cada red tendría funciones distintas y se localizaría en zonas diferentes del cerebro (Posner y Petersen, 1990; Posner y Rothbart, 1991; Posner y Dehaene, 1994).

Una de las funciones más destacadas de la Red Atencional Posterior sería la de orientar la atención hacía los estímulos relevantes del ambiente (Posner, 1980; Posner y Cohen, 1984). Gracias a esta función, la rapidez y precisión de un sujeto es mayor a la hora de percibir un estímulo señalado previamente (ensayo válido en el PCCP), en comparación con uno inesperado (ensayo inválido en el PCCP) (Figura 2). La orientación atencional previa hacía el estímulo esperado facilita su percepción y procesamiento. Las áreas cerebrales implicadas en este proceso parecen ser el córtex parietal posterior (con predominancia en el lado derecho), los núcleos pulvinar y reticular del tálamo y los colículos superiores (Rafal y col., 1991; Friedrich y col., 1998; Corbetta y col., 2000). El núcleo pulvinar estaría implicado concretamente en la supresión de los posibles estímulos irrelevantes y la potenciación de las señales significativas (Robinson, 1993). La clave produciría en última instancia la activación de las cortezas sensoriales y motoras contralaterales al lugar señalizado por la clave, facilitando el procesamiento sensoriomotor si la clave es válida, y provocando la reorientación atencional si la clave es inválida (Gómez y col., 2004).

Por su parte, la Red Atencional de Vigilancia o Alerta se encargaría de que el sujeto mantenga el nivel de arousal (estado de preparación) necesario para la detección de los estímulos relevantes. Tanto el estado de alerta duradero (necesario para tareas de vigilancia), como la alerta fásica o de corta duración (provocado por una señal que indica la llegada inminente de un estímulo) se atribuyen a esta red atencional (Posner y col., 1973). Los diferentes estudios realizados muestran que las áreas corticales asociadas a esta función de alerta estarían lateralizadas en el hemisferio derecho y en los lóbulos frontales y parietales (Posner y Petersen 1990). Concretamente, la activación de esta red dependería del sistema reticular y sus aferencias con el tálamo, el sistema límbico, así como zonas frontales y de los ganglios basales. Una patología en este sistema derivaría en estados confusionales, comatosos o de hipervigilia.

La Red Atencional Anterior sería la que permite llevar a cabo un control voluntario de la atención cuando la situación requiere planificación, desarrollo de estrategias, resolución de conflictos, generación de respuestas novedosas, etc. (Posner y Raichle, 1994), estando bastante relacionada con el funcionamiento de la memoria de trabajo (Posner y Dehaene, 1994). Los diferentes estudios realizados coinciden en que las estructuras cerebrales relacionadas con el funcionamiento de esta red serían el cíngulo anterior y diferentes áreas prefrontales (MacDonald y col., 2000). Sin embargo, existen modelos más recientes que proponen una distinción entre al menos dos subsistemas encargados de estas funciones ejecutivas; por un lado, Corbetta y Shulman (2002) proponen un subsistema encargado de procesar la novedad y la estimulación destacada (formado por el córtex temporoparietal y el córtex frontal inferior derecho) y otro responsable del desarrollo de las expectativas (formado por el córtex intraparietal y el

córtex frontal superior); y por otro lado, Botvinick y col. (1999/2001) distinguen entre la función ejecutiva de detección/resolución de conflictos de respuesta y la encargada de otros procesos como la selección de información relevante. La disfunción de esta red podría desembocar en síntomas como perseveraciones, distractibilidad o problemas de concentración, siendo el TDAH un posible trastorno generado por este sistema (Swanson y col., 1991).

Dentro de este contexto, la teoría atencional de Posner plantearía un triple sistema formado por estas tres redes anatómica y funcionalmente diferentes, pero interconectadas entre sí. Dicha teoría otorgaría un papel esencial a la llamada Red Atencional Anterior, debido a su capacidad para modular a las otras dos redes cuando las tareas requieren el desarrollo de estrategias para predecir el comportamiento de los estímulos.

Para desarrollar y evaluar su teoría, Posner planteo un paradigma que permitiese poner en practica el funcionamiento del sistema atencional. El Paradigma de las Claves Centrales de Posner (PCCP), o simplemente paradigma de Posner, sería un test neuropsicológico que evalúa la capacidad del individuo para llevar a cabo cambios atencionales (Posner, 1980). Este paradigma se puede usar para medir tanto respuestas conductuales (tiempos de reacción a nivel manual u ocular, comisión de errores a la hora de responder a los estímulos, etc.) como neurológicas (por ejemplo a través de un registro de EEG mientras el sujeto realiza la tarea).

En general, para realizar el PCCP, los sujetos están sentados delante de un monitor. La primera instrucción que reciben consiste en fijar la mirada en un punto o una cruz situada en el centro de la imagen, mientras realizan la tarea. A cada lado de dicha

cruz habría un cuadrado. A continuación, se les explica que en cada ensayo aparece una señal (normalmente una flecha encima de la cruz) que les indica el cuadrado de la derecha o el de la izquierda, y, tras la señal, aparece un estímulo dentro de uno de los dos cuadrados (por ejemplo una estrella), de modo que deben responder (con un aparato de respuesta que tendrá dos opciones: derecha e izquierda) al botón derecho si el estímulo aparece en el cuadrado derecho, y al botón izquierdo si aparece en el izquierdo (Figura 2). Una vez que han respondido, hay un breve período de descanso entre-ensayos (suele variar entre 2500 y 5000 milisegundos), y tras éste, vuelve a comenzar un nuevo ensayo con la misma dinámica. En base a este esquema el experimentador puede variar tanto el número total de ensayos que son presentados, como el porcentaje de ensayos válidos (la señal indica correctamente el cuadrado en el que aparece el estímulo objetivo) e inválidos (la señal indica el lado opuesto al cuadrado en el que aparece el estímulo objetivo) que habrá en cada bloque de ensayos (Bashinski y col., 1980).

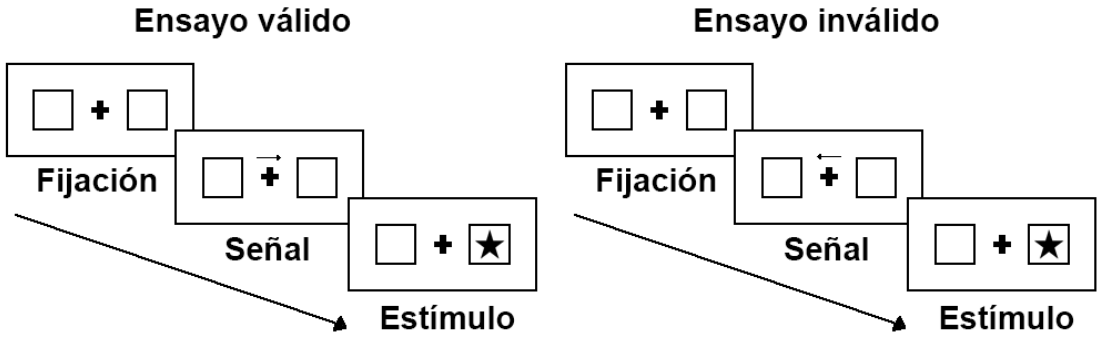

Figura 2. Paradigma de las Claves Centrales de Posner (PCCP). Ejemplo de ensayo válido e inválido.

En los estudios originales de Posner se emplearon tareas que contaban en general con un 80% de ensayos válidos y un 20% de ensayos inválidos (se incluían ensayos neutros (sin clave previa)) (Posner, 1980). De esta forma, el sujeto aprendía que la clave

iba a ser correcta en la mayoría de los casos y se creaba una tendencia a orientar la atención hacia el lado indicado. Gracias a esta orientación atencional previa, los sujetos mejoraban la velocidad y precisión de respuesta en los ensayos válidos, pero también tardaban más en responder en los ensayos inválidos, debido a que tenían que reorientar su foco atencional desde el lado indicado al opuesto (Posner y col., 1978; Posner y col., 1980).

Muchas variantes del PCCP han sido usadas en años posteriores con el objetivo de evaluar las habilidades atencionales en diferentes síndromes, así como para entender un poco mejor el funcionamiento de la atención espacial en sujetos sanos. Gracias a estos estudios se han podido constatar, entre otras ideas, (i) que los daños en el lóbulo parietal pueden afectar a la capacidad de reorientar la atención en ensayos inválidos (Posner, Walker y col., 1984); (ii) que los niños diagnosticados con Déficit de Atención e Hiperactividad presentan tiempos de reacción más lentos en ensayos válidos e inválidos (especialmente cuando el estímulo target aparece en el campo visual izquierdo) (McDonald y col., 1999); y (iii) que el funcionamiento de la atención con claves pierde precisión y velocidad con la edad (Langley y col., 2011).

Volviendo a las 3 redes atencionales, cabe señalar que El PCCP se relacionaría especialmente con la red anterior o ejecutiva, mientras que el Paradigma de Claves Periféricas lo haría con la red posterior o de orientación. En el caso de la red de alerta se podría usar para estudiarla una señal de aviso central no direccional. En este sentido, por medio del llamado paradigma ANT (Attentional Network Test) se ha operacionalizado la medida de las tres redes simultáneamente (Redick y col., 2006; Marrufo y col., 2011).

> El cerebro 'Bayesiano'

La estadística bayesiana (Clark, 2013) es una aproximación teórica desde la cual se ha tratado de explicar el funcionamiento del cerebro. Concretamente, se ha investigado la capacidad del sistema nervioso para operar en situaciones de incertidumbre, de forma que se optimicen al máximo los recursos siguiendo principios estadísticos. La idea establecería que el sistema nervioso funciona a través de modelos probabilísticos (probabilidad bayesiana (Knill y col., 2004; Doya y col., 2007)) que se van actualizando en base a la información sensorial recibida por el cerebro. El concepto conocido como 'cerebro bayesiano' (Hinton y col., 1983) define el cerebro como un sistema que está constantemente calculando probabilidades y haciendo predicciones acerca de los sucesos que le rodean. Dichas predicciones se realizan en base a la experiencia o la información sobre el ambiente obtenida hasta el momento y pueden actualizarse (reevaluarse y corregirse o modificarse) en función de los sucesos nuevos que vayan ocurriendo. De esta forma el cerebro está continuamente adaptándose al medio que lo rodea.

Esta aproximación teórica tiene su origen en trabajos como el de Hermann Helmhotz en el campo de la Psicología Experimental del siglo XIX, donde estableció un modelo de funcionamiento del cerebro basado en la extracción de información sensorial siguiendo estimaciones probabilísticas. En 1983 Geoffrey Hinton y sus colaboradores (Fahlman y col., 1983) propusieron que el cerebro podía ser entendido como un sistema que toma decisiones en base a las incertidumbres del mundo que le rodea. Años más tarde, Jaynes (1988) presentó un trabajo donde establecía la estructura para usar la estadística bayesiana como modelo del procesamiento mental. A partir de aquí, durante la década de 1990 diferentes autores, basándose en los conceptos iniciales de Helmholtz, reportaron

ideas sobre cómo el cerebro crea una representación del funcionamiento del mundo exterior en términos de probabilidades (Dayan y col., 1995; Hinton y col., 1995; Dayan y Hinton, 1996).

El conocido como 'principio de la energía libre' (free energy principle) trata de explicar como los sistemas biológicos minimizan la energía libre de sus estados internos en base a las creencias sobre el estado de su ambiente. Este principio estaría relacionado con los métodos bayesianos y fue propuesto originalmente por Friston y col., (2006) como una explicación sobre la percepción de los estímulos en neurociencia (usando el concepto de inferencia activa). Friston desarrolla una teoría matemática (Friston, 2009/2010) que está considerada por muchos como la más acertada a la hora de intentar crear una teoría general que explique el funcionamiento del cerebro. Basándose en la idea previa del 'cerebro bayesiano', establece que la acción y la percepción van dirigidas a optimizar la actividad neuronal y neuromuscular a través de los datos sensoriales, de forma que se eliminen los errores de predicción. En otras palabras, a través de la acción y la percepción se corregirían las predicciones erróneas y se intentaría reducir constantemente al mínimo la llamada energía libre o energía desaprovechada.

> Electroencefalografía: registro de la actividad eléctrica cerebral

En la actualidad se puede encontrar una amplia variedad de métodos que permiten evaluar las capacidades cognitivas en seres humanos. Existen técnicas que basan sus resultados en parámetros puramente conductuales (como las diferentes pruebas que se pueden usar en una evaluación neuropsicológica, o en experimentos de tiempos de reacción) y otras que analizan el funcionamiento neural a través de la medición de

diferentes patrones que correlacionan con el estado funcional del cerebro durante la realización de tareas cognitivas (Electroencefalografía (EEG), Tomografía por Emisión de Positrones (TEP), Resonancia Magnética funcional (IRMf), Magnetoencefalografía (MEG) y la Near-infrared spectroscopy (NIRS)).

El electroencefalograma (EEG) continua ocupando un lugar destacado dentro del campo de los métodos de diagnóstico clínico y experimentales. Entre otras ventajas, esta técnica (i) proporciona a los investigadores un registro de la actividad eléctrica cerebral de gran resolución temporal (permitiendo captar la actividad de poblaciones neuronales en milisegundos); (ii) no es invasiva; y (iii) resulta relativamente económica.

La invención del EEG, como técnica de registro de la actividad eléctrica cerebral en humanos, data del año 1924, cuando el neurólogo alemán Hans Berger hizo el primer registro de las oscilaciones rítmicas del cerebro humano usando un galvanómetro. Sin embargo, su historia se remonta mucho antes. Considerando el EEG como una manifestación de los ritmos eléctricos del cerebro, ya en el año 1770, el médico italiano Luigi Galvani reportó observaciones de actividad eléctrica en animales. Por otro lado, las primeras descripciones sobre la existencia de actividad eléctrica en el cerebro se atribuyen al fisiólogo inglés Richard Caton, quien en 1875 publicó sus observaciones sobre actividad cerebral continua y espontánea y se habló de "corrientes eléctricas en la sustancia gris".

La señal registrada a través del EEG contiene la actividad eléctrica de diferentes grupos de poblaciones neuronales en distintas áreas cerebrales. Estos grupos de neuronas generan corrientes iónicas que fluyen a través de las membranas neuronales, causando

campos eléctricos y magnéticos que son registrados y medidos. El registro obtiene la secuencia de oscilaciones que aparece en la diferencia de voltaje entre los electrodos situados en el cuero cabelludo.

Generalmente, se emplean dos tipos de medición a la hora de registrar la actividad cerebral humana. Por un lado, se pueden estudiar las fluctuaciones espontáneas de voltaje que genera el cerebro sin estar involucrado en ninguna actividad aparente (sin que tenga relación con un acontecimiento específico), conocidas como 'ritmos cerebrales espontáneos' o 'EEG espontáneo'. Por otro lado, se analizan las fluctuaciones de voltaje en la actividad eléctrica cerebral originadas por eventos o estímulos sensoriales. Estas variaciones serían el reflejo de la respuesta de diferentes regiones del cerebro ante la percepción y el procesamiento de estímulos externos. Se conocen como Potenciales Relacionados con Eventos (PREs) y podrían ser cuantitativamente caracterizados por su amplitud, polaridad, latencia y distribución en el cuero cabelludo.

Tanto para el registro del EEG espontáneo, como para el de los PREs, se suelen posicionar los electrodos sobre la cabeza en base al conocido Sistema Internacional 10-20 (Jasper, 1958) (Figura 3). Este sistema define la localización de cada electrodo empleando dos coordenadas: por un lado, la proximidad a un área concreta del cerebro (frontal, central, temporal, parietal y occipital); por otro lado, la ubicación en el plano lateral (números impares a la izquierda, números pares a la derecha y la letra z para los electrodos centrales). A parte de usar estas localizaciones pre-definidas, existe la posibilidad de colocar otros electrodos en zonas concretas del cuero cabelludo porque interesen especialmente dentro de un estudio (por ejemplo en el área de Broca).

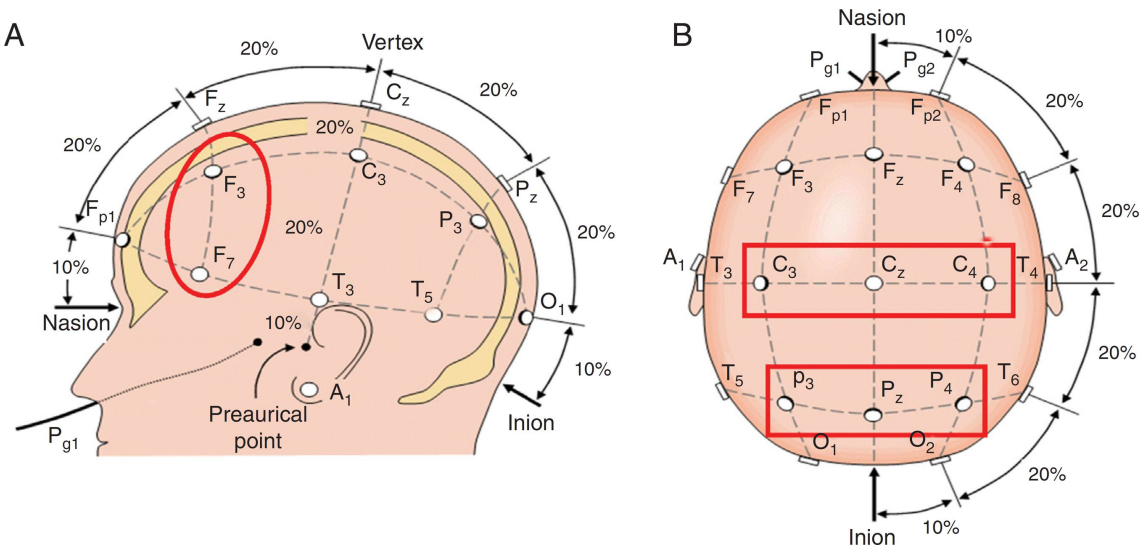

Figura 3. Sistema Internacional estándar de colocación de electrodos 10-20

> *Potenciales Relacionados con Eventos (PREs)*

Los PREs son respuestas electrofisiológicas vinculadas al procesamiento específico de un evento sensorial, cognitivo o motriz. Dichas respuestas reflejan las características espaciales y temporales de los sistemas neurales que intervienen. Se trata concretamente de una serie de oscilaciones de voltaje (entre 1 y 20 microvoltios), provocadas por la actividad eléctrica de las neuronas (la suma de potenciales post-sinápticos generados por los procesos de despolarización e hiperpolarización), cuya resolución temporal es del orden de milisegundos. El registro, mediante EEG, de estos potenciales permite medir los cambios de voltaje con una alta resolución temporal, sin embargo, la resolución espacial (necesaria para identificar el origen neuronal) es bastante baja en comparación con otras técnicas como la TEP o la IRMf. Este defecto es debido a lo que se conoce como el problema inverso, que establece que si tenemos una distribución de potencial eléctrico a lo largo de un cuerpo conductor, como es la cabeza, no podemos saber exactamente de donde provienen los potenciales, si no sabemos a priori el número de generadores que hay activos (Grave de Peralta, 2004; Urrestarazu, 2005). En el caso

de los PREs, se debe realizar una estimación indirecta del origen neuronal de las señales en base a la distribución de voltaje en la superficie del cuero cabelludo.

A cada uno de los diferentes PREs que se registran en un estudio se les conoce como componentes. Un componente puede definirse en base a una combinación de características como son la polaridad (positiva o negativa), latencia (medida en milisegundos (ms) desde la presentación del estímulo hasta el punto de máxima amplitud del componente), topografía (distribución en el cuero cabelludo) y sensibilidad experimental (especificidad a la hora de ser provocado por una determinada manipulación experimental) (Donchin y col., 1978).

Los PREs pueden estar relacionados con diferentes aspectos del procesamiento que realiza la corteza cerebral ante la percepción de un estímulo. A través del registro y la medición de estos potenciales, se pueden obtener indicadores tanto de procesos neurológicos normales como patológicos. Los diferentes PREs se distinguen entre ellos principalmente en base su polaridad topográfica y su latencia temporal, reflejando cada uno diferentes fases o momentos en el procesamiento de los estímulos percibidos. Una de las divisiones conocidas de los PREs los separa en dos grandes grupos (Carretié, 2001):

1. Componentes exógenos: son conocidos también como ondas tempranas, ya que tienen una latencia de entre 100 y 150 ms tras la presentación del estímulo. Por otro lado, son componentes que están modulados por las características físicas dicho estímulo (la modalidad de presentación (auditiva, visual, etc.) o la intensidad). La latencia de estos componentes suele usarse como prueba de diagnóstico estandarizado para enfermedades de origen neurológico.

2. Componentes endógenos: llamados también ondas tardías, suelen aparecer entre los 200 y 500 ms tras la presentación del estímulo. Son componentes más relacionados con procesos cognitivos (atención, memoria, etc.), con la relevancia de la tarea para el sujeto o con su estado de activación.

Cabe destacar sobre esta dicotomía que, según diferentes autores, sería más correcto hablar de un continuo exógeno-endógeno (Coles y Rugg, 1995). En este sentido, se ha observado como muchos componentes exógenos se ven modificados por manipulaciones cognitivas, mientras que los componentes endógenos también varían en función de las características físicas del estímulo. Coles y Rugg (1995) hacen además una distinción entre componentes previos y posteriores a la ocurrencia del suceso objetivo (target). Dentro de los componentes previos se pueden incluir la variación negativa contingente (Contingent Negative Variation -CNV-) y el potencial lateralizado de preparación (Lateralized Readiness Potential -LRP-); mientras que los componentes posteriores pueden ser el P1 y N1 (visual o auditivo), el P2 (anterior y posterior), la negatividad de procesamiento (Processing Negativity -PN-) o el P300 (anterior y posterior).

a) Contingent Negative Variation (CNV)

La CNV es una onda de polaridad negativa, gran amplitud y latencia lenta y tardía que está relacionada con la expectativa o la preparación (Walter y col., 1964; Rockstroh y col., 1982). Por lo tanto, este componente tendría lugar entre la percepción de un estímulo de aviso que nos prepara o alerta sobre la llegada de otro estímulo y la aparición del estímulo esperado. Se trata de un componente que ha sido relacionado tanto con el

mantenimiento de la atención en una tarea, como con la preparación de respuestas motoras (Eimer, 1993; Gómez y col., 2004). A través de diferentes estudios, esta onda negativa ha sido localizada en zonas fronto-centrales y posteriores dentro del cerebro (Cui y col., 2000; Gómez y col., 2001; Zappoli y col., 2000), y se han reportado casos de asimetría hemisférica (Butler y col., 1974; Kutas y col., 1980; Lutzenberger y col., 1985; McCarthy y col., 1978).

A través de diferentes estudios, que han empleado paradigmas con claves, se ha ido estudiando esta onda negativa relacionada con la pre-activación sensorio-motora necesaria para realizar adecuadamente las tareas (Brunia y col., 2001; Flores y col., 2009; Gómez y col., 2001/2004; Mento, 2013; Mento y col., 2013). El paradigma experimental clásico utilizado para estudiar la CNV consiste en la presentación de un estímulo clave o estímulo de aviso (S1) seguido, tras un intervalo relativamente corto de tiempo, de un estímulo target o estímulo imperativo (S2). En base a este esquema, la CNV se desarrollaría aproximadamente a partir de los 300-500 ms tras la presentación del estímulo S1 y, en función de la duración del período de demora, puede alargarse hasta varios segundos. El pico de máxima amplitud de la onda rondaría los 20 microvoltios, y, en función de la certeza que tenga el sujeto sobre el momento exacto en el cual aparecerá el estímulo S2, la negatividad aparecerá con mayor rapidez (mayor incertidumbre) o más gradualmente (menor incertidumbre). Tras la llegada de S2, suele requerirse algún tipo de respuesta por parte del sujeto (física o mental) para poder generar una CNV clara (Tecce, 1972). El estímulo S1 actuaría como una señal que dispara la activación de las áreas necesarias para el procesamiento de S2, así como para preparar la posible respuesta motora o cognitiva (Gómez y col., 2003/2004). Desde la perspectiva de la "Teoría de la regulación del umbral" la negatividad se interpretaría como un incremento de la pre-

activación neuronal por medio de la despolarización de las dendritas apicales de las neuronas piramidales (Rockstroh y col., 1993).

Mediante la variación del período que transcurre entre S1 y S2, se ha comprobado que la CNV es un proceso en el que se pueden distinguir al menos dos fases: una primera fase más temprana, que estaría relacionada con la respuesta de orientación generada por S1, y una segunda fase más tardía, que reflejaría la preparación de la respuesta (motora, sensorial y/o cognitiva) (Loveles y col., 1974; Gaillard, 1977; Rohrbaugh y col., 1983/1976). Más recientemente, la fase tardía se ha relacionado también con la preparación de las áreas neurales necesarias para el procesamiento sensorial de S2 (Brunia y col., 2001; Flores y col., 2009; Gómez y col., 2004).

La fase más temprana de la CNV tendría una distribución frontal bilateral y, al estar relacionada con el procesamiento del estímulo S1, su amplitud dependería de la intensidad de dicho estímulo. En cambio, la fase más tardía de la CNV (cercana a la llegada el S2) se localizaría en regiones más centrales y, en el caso de paradigmas de respuesta manual, en el hemisferio contralateral a la mano usada para emitir la respuesta. Estaría relacionada no solo con la expectativa psicológica, sino también con la preparación de las áreas motoras necesarias para emitir la respuesta requerida. En este punto, estaríamos también hablando de otro potencial conocido como Lateralized Readiness Potential (LRP) (Rockstroh, 1982; Cui y col., 2000; Gómez y col., 2001/2003).

La utilidad del estudio de la CNV no se limitaría únicamente al aprendizaje del funcionamiento neural (indicando la capacidad de generar un estado de preparación en los sujetos), sino que su estudio es aplicable a investigaciones relacionadas con diferentes

trastornos neurales, como el TDAH (Perchet y col., 2001).

b) Lateralized Readiness Potential (LRP)

La LRP es un componente que indica la preparación de las áreas motoras para emitir una respuesta. Estaría relacionado con el proceso de activación necesario para seleccionar la respuesta que se quiere emitir. A nivel experimental, se trataría de un componente que suele observarse cuando los sujetos tienen que elegir entre responder con la mano izquierda o derecha a lo largo de los diferentes ensayos (Kappenman y col., 2012). Reflejaría la activación motora generada por el estímulo de aviso (S1) para responder al estímulo objetivo (S2) (Gehring y col., 1992; Arjona y col., 2014b).

La introducción de este componente en la literatura científica comenzó en el año 1988 a través de las investigaciones de diferentes grupos (De Jong y col., 1988; Gratton y col., 1988), siendo el grupo de Gratton quien le dio su nombre actual. Se trata, básicamente, de potenciales que precedían los movimientos de las extremidades, y que ya habían sido descritos unos años antes por Kornhuber y col., (1965), quienes encontraron una onda negativa que incrementaba gradualmente durante el segundo previo a la iniciación de un movimiento con las manos. Este potencial comienza siendo simétrico entre ambos hemisferios, pero, cuando se acerca el momento de emitir la respuesta, se amplia alrededor de la corteza motora del hemisferio contralateral a la mano de respuesta (Kutas y col., 1980). Algunos autores describieron este potencial como una CNV (Syndulko y col., 1977) y no esta aún completamente claro si la última fase de la LRP y la CNV reflejan procesos equivalentes o funcionalmente diferentes (Rohrbaugh y col., 1983; Van Boxtel, 1994).

Para el estudio de la LRP mediante EEG, se suelen analizar las zonas cercanas a la corteza motora, alrededor de los electrodos centrales (Gratton y col., 1988; Smulders y col., 1995). A pesar de ello, en algunos experimentos (Miller y col., 1992) se ha observado que esta onda puede considerarse parcialmente independiente de la ejecución motora de la respuesta, ya que aparece en tareas en las que se genera un plan de respuesta, pero al final no se ejecuta. Otros investigaciones han relacionado este componente con la transmisión de información entre el proceso de percepción y la respuesta (Gómez y col., 2011).

c) Componente N1 (visual y auditivo)

El potencial evocado conocido actualmente como N1 o N100 consta como registrado por primera vez por la investigadora Pauline A. Davis en la Universidad de Harvard (Davis, 1939). El origen de este potencial fue desconocido en sus inicios y varias décadas más tarde se asoció a la actividad de la corteza auditiva (Vaughan y col., 1970).

El componente N1 se caracteriza por presentar una acentuada polaridad negativa, cuyo punto máximo se sitúa entre 80 y 120 milisegundos tras la presentación del estímulo objetivo (S2) (Hillyard y col., 1973; Arjona y col., 2014a). Este componente se manifestaría alrededor de la zona fronto-central del cerebro y se ha observado tras una amplia variedad de modalidades de presentación de estímulos (Pause y col., 1996; Quant y col., 2005; Wang y col., 2008), siendo las modalidades visual (Vogel y col., 2000; Doallo y col., 2005) y auditiva (Näätänen y col., 1987; Arjona y col., 2017) las más usadas.

El llamado componente N1 auditivo (generado tras la aparición de un target auditivo) tendría su origen en redes neuronales localizadas dentro de la corteza auditiva primaria, el giro temporal superior, área de Heschl e incluso zonas motoras frontales (Näätänen y col., 1987; Zouridakis y col., 1998; Godey y col., 2001). En el EEG puede verse precedido por un componente P1, el cual aparece más claramente cuando se registra en niños (Mahajan y McArthur, 2012). Además, se ha observado una mayor actividad de este componente en el hemisferio derecho en comparación con el izquierdo. Sería un potencial relacionado con los procesos de preparación sensorial y atencional generados con el fin de percibir un estímulo auditivo. En este sentido, diferentes estudios han mostrado un incremento de N1 ante la percepción de estímulos esperados, en comparación con los estímulos inesperados (Parasuraman, 1980; Woldorff y Hillyard, 1991; Woldorff y col., 1993; Fabiani y col., 2000; Arjona y col., 2017). Por otro lado, se ha observado que su amplitud estaría posiblemente afectada por las características del estímulo auditivo (potencia, frecuencia, novedad, etc.) (Keidel y col., 1965; Davis y col., 1966; Butler, 1968; Spreng, 1980), así como por el nivel de arousal de la persona que lo genera (Nash y col., 1982).

A nivel del desarrollo cerebral, el componente N1 tendría una aparición bastante progresiva. Durante la niñez avanzada empezaría a desarrollarse un potencial negativo alrededor de los 200 milisegundos que se manifestaría hasta la adolescencia. Este potencial sería equivalente al N1 de los adultos tanto en su topografía como en la forma de generarse. Además, con respecto al desarrollo en ambos hemisferios cerebrales, se ha observado una maduración más rápida de este componente en el hemisferio izquierdo en comparación con el hemisferio derecho (Pang y col., 2000).

Con respecto al uso de este componente en el ámbito clínico, cabe destacar su aplicación para detectar anomalías en el sistema auditivo en casos en los que los pacientes no pueden emitir respuestas verbales o conductuales (pacientes en coma o sedados) (Hyde, 1997; Fischer y col., 2000/2004). Por otro lado, diferentes estudios han asociado cambios en la manifestación del componente N1 con diferentes trastornos cognitivos como la dislexia, esquizofrenia, etc. (Hanlon y col., 2005; Shaul, 2007).

d) Componente P2

El componente conocido como P2 o P200 es un potencial de polaridad positiva que se caracteriza principalmente por presentar su pico máximo de actividad unos 200 milisegundos (con una variabilidad de unos 50 milisegundos) tras la aparición de un estímulo externo (visual, auditivo, etc.). A nivel topográfico se ha reportado su pico máximo alrededor de las regiones centrales (Cz), con desplazamientos a zonas frontales y parieto-occipitales del cuero cabelludo (Tremblay y col., 2001/2009; Freunberger y col., 2007). En base a las diferentes investigaciones realizadas hasta ahora, la interpretación más amplia sobre el significado funcional de este componente establece que representaría algún aspecto del procesamiento perceptual del estímulo y que, por tanto, estaría modulado por la atención. También podría estar relacionado con el proceso de comparación entre la información sensorial recibida (visual, auditiva, etc.) y el almacén de memoria (Ford y col., 1976; Vaughan y col., 1980; Luck y col., 1994; Oades y col., 1997; Crowley y col., 2004; Freunberger y col., 2007).

Originalmente, el potencial P2 fue considerado como un subcomponente perteneciente a lo que se llamó el potencial del vértex (incluyendo P1, N1 y P2, que serían 3 potenciales auditivos que ocurren consecutivamente tras la presentación de un estímulo). En este sentido, la diferencia entre el pico de N1 y P2 llegó a ser conocida como la amplitud del vértex (Furutsuka, 1989). Sin embargo, estudios posteriores examinaron el componente P2 de forma aislada y encontraron que presentaba una mayor amplitud tras la aparición de estímulos menos frecuentes (Luck y col., 1994). Con respecto a los estudios con estímulos auditivos, destacan los reportes que muestran una mayor amplitud del componente P2 tras la repetición del mismo estímulo, relacionándolo con el aprendizaje (Tremblay y col., 2001; Shahin y col., 2003).

Actualmente, la dificultad principal que impide concretar cuáles son los procesos neurales que subyacen a la aparición del componente P2 sería la amplia variedad de factores que afectan a las características del mismo (frecuencia de aparición del estímulo que lo genera, forma de presentación, color, tamaño, etc.). En este sentido, destacan investigaciones que muestran la relación entre la amplitud del P2 y el funcionamiento de la working memory o los procesos de reconocimiento (Dunn y col., 1998; Lefebvre y col., 2005). Por otro lado, también se ha reportado la implicación del P2 en procesos relacionados con el lenguaje (Federmeier y col., 2002/2005; Wlotko y col., 2007).

En base a diferentes investigaciones se ha propuesto que el componente P2 podría tener bastante utilidad para la práctica clínica. Concretamente, en casos de pacientes que padecían demencia o Alzheimer se han observado diferencias significativas con respecto a la latencia y amplitud de este componente en zonas posteriores. Estos datos indicarían

que el registro de este componente puede servir como herramienta para el diagnóstico precoz de estas enfermedades (Moore y col., 1995; Arruda y col., 2002).

e) Negatividad de Procesamiento (Processing Negativity (PN))

La PN es una onda de polaridad negativa que (empleando tareas basadas en la discriminación de diferentes modalidades de estímulos) se ha asociado con el funcionamiento de la atención selectiva y la working memory; concretamente, estaría relacionada con el esfuerzo atencional para seleccionar el estímulo a procesar (Näätänen y col., 1978). Además, en la modalidad de estímulos auditivos, la PN ha sido dividida en dos componentes; un componente fronto-central temprano que se genera en la corteza auditiva (early PN) y otro frontal y más tardío (late PN) (Hansen y col., 1980; Näätänen, 1982; Giard y col., 1988; Woldorff y col., 1993).

Diferentes estudios atencionales mencionan la posibilidad de un solapamiento de la PN sobre los componentes N1 y P2 (que ocurren en el mismo rango de latencia) a la hora de procesar estímulos atendidos (Näätänen y col., 1978/1979; Michie y col., 1990). En este sentido, la PN sería un indicador del esfuerzo atencional realizado por el sujeto para seleccionar un determinado estímulo.

f) Componente P300 (P3a y P3b)

El componente P3 o P300 es un potencial de polaridad positiva cuyo rango de latencia se suele situar entre 250 y 500 milisegundos tras la aparición de un estímulo al que el sujeto debe responder. Presenta una amplitud inversamente proporcional a la

probabilidad de aparición del estímulo (Duncan-Johnson y col., 1982; Squires y col., 1976), y, en base a las diferentes investigaciones, este potencial se ha relacionado con procesos como la evaluación de lo ocurrido o la actualización de la memoria de trabajo (Donchin y col., 1988; Polich, 2007).

La primera vez que se reportó el registro del potencial que hoy conocemos como P300 fue hace aproximadamente hace 50 años (Sutton y col., 1965). Más tarde, el llamado 'Paradigma de Oddball' fue clave a la hora de relacionar la amplitud de este componente con la probabilidad de ocurrencia del estímulo objetivo, así como con la relevancia de la tarea (Donchin y col., 1978; Pritchard, 1981). En dicho paradigma, la amplitud del componente P300 indicaría la activación neural relacionada con la actualización de la representación mental sobre el estímulo objetivo. De este modo, cuando un estímulo novedoso o inesperado aparece, el mecanismo atencional se activaría para conducir un proceso de evaluación que tiene lugar en la memoria de trabajo con el fin de actualizar la información sobre la representación del estímulo objetivo (Donchin, 1981; Heslenfeld, 2003; Kujala y col., 2003).

A pesar de que el P300 resulta fácilmente replicable mediante paradigmas como el de Oddball o el Paradigma de las Claves Centrales de Posner (PCCP), no existe aún un entendimiento claro sobre cómo y por qué se produce dicho potencial. En otros estudios relacionados con procesos de memoria y reconocimiento, se observa una mayor amplitud del P300 cuando aparecen estímulos que ya se habían visto antes, en comparación con estímulos nuevos (Rugg y col., 1992; McEvoy y col., 2001). Por otro lado, también se ha observado que la variación del intervalo entre estímulos afecta a la amplitud del P300 (Mertens y col., 1997; Polich y col., 1994), así como la participación de la memoria en la

tarea (Azizian y col., 2007). En este sentido, las teorías que relacionan el P300 con los procesos de actualización de la memoria de trabajo y el procesamiento atencional serían las más extendidas por su versatilidad para adaptarse a los diferentes resultados (Isreal y col., 1980; Wickens y col., 1983; Donchin y col., 1986).

El P300 es un componente que, desde sus inicios, se ha dividido en dos subcomponentes: el P3a y el P3b. El subcomponente conocido como P3a presentaría una topografía más fronto-central, y un pico de latencia en el rango entre 250 y 280 milisegundos tras la aparición de un estímulo objetivo. Se trataría de un potencial relacionado con el procesamiento atencional de dicho estímulo (especialmente con la orientación), y de la posible novedad asociada a su llegada (Friedman y col., 2001). Por su parte, el P3b se referiría a una positividad más posterior, que aparece aproximadamente tras unos 300 milisegundos (variando entre 250 y 500 milisegundos) desde la aparición del estímulo objetivo. Este subcomponente ha sido muy útil a la hora de estudiar diferentes procesos cognitivos como el procesamiento de la información. Es un potencial que aumenta en función de lo inesperado que resulte el estímulo que lo genera y de la cantidad de atención prestada por el sujeto a dicho estímulo. El significado funcional de este potencial se relacionaría con el proceso de actualización del almacén de memoria del sujeto, cuyo objetivo final sería mejorar la predicción sobre la posterior aparición de estímulos relevantes (Squires y col., 1975; Donchin, 1981; Comerchero y col., 1999; Friedman y col., 2001; Kok, 2001; Gaeta y col., 2003; Hartikainen y col., 2003).

A nivel de localización, existen diferentes estudios de pacientes con lesiones cerebrales que han arrojado luz sobre las posibles fuentes neurales del P300. En este sentido, se ha reportado que las lesiones en el lóbulo frontal provocan una disminución

de la amplitud del P3a, pero no del P3b, indicando que éste último presentaría un origen más posterior. Además, la reducción del P3a se ha observado tras lesiones tanto en la corteza prefrontal lateral, como en la corteza orbitofrontal (Løvstad y col., 2012). Por otro lado, lesiones en la unión temporo-parietal se han relacionado con disminución de la amplitud en ambos componentes. En suma, el P3a parece presentar una mayor dependencia de las zonas frontales, mientras que el P3b parece tener un origen más posterior (Bledowsky y col., 2004).

Las aplicaciones prácticas que se han estudiado hasta ahora con respecto a el análisis del P300 han sido varias. Por un lado, la manifestación de este potencial ha sido investigada como una forma de detectar si los sujetos mienten o no (Farwell y col., 2001), sin haberse llegado aún a un acuerdo sobre su utilidad. Por otro lado, el P300 se ha propuesto como un potencial idóneo para la implementación y el estudio de interacciones directas entre el cerebro y un aparato externo (brain-computer interfacing) (Donchin y col., 2000; Piccione y col., 2006). Finalmente, algunos investigadores han sugerido que este potencial puede ser útil en el ámbito clínico para medir la eficacia de los diferentes tratamientos aplicados a sujetos con déficit cognitivo (Hansenne, 2000).

g) Onda Negativa Lenta (Negative Slow Wave (NSW))

Diversos estudios de Potenciales Relacionados con Eventos (PREs) han mostrado la aparición de esta onda negativa (NSW) en zonas frontales, y con una latencia similar a la del P3b (Van Leeuwen y col., 1998; Flores y col., 2009). En algunos casos, particularmente en los estudios con niños, se ha argumentado que esta negatividad correspondería al lado opuesto de un dipolo positivo en zonas posteriores. Sin embargo,

gracias a un estudio donde se disociaron los efectos sobre el P3b y la NSW provocados por una lesión en la corteza prefrontal dorsolateral (Lovstad y col., 2012), se demostró que la NSW (en su modalidad auditiva) tendría un origen únicamente frontal. Desde un punto de vista funcional, Rohrbaugh y col. (1979) asociaron la NSW con respuestas de orientación y alerta, como la registrada por Walter y col. (1964) en la latencia de la CNV temprana, generada por el estímulo de alerta (S1). Por su parte, Wetzel y col. (2014) describieron la NSW como una onda relacionada con el esfuerzo de reorientación que se genera ante estímulos distractores (negatividad de reorientación).

- Objetivos e hipótesis

> Objetivos

El objetivo principal que trata de abordar la presente Tesis Doctoral consiste en el estudio de los Potenciales Relacionados con Eventos (PREs) que participan en la realización de una versión auditiva del Paradigma de las Claves Centrales de Posner (PCCP). Se espera que las modulaciones registradas en los PREs vayan en consonancia con los datos que se obtengan sobre los patrones de respuestas conductuales en las diferentes condiciones. Por medio del análisis de los PREs y de las respuestas conductuales a claves válidas e inválidas (que a su vez están precedidas por una historia concreta de validez e invalidez) se pretenden describir los posibles mecanismos neurales a través de los cuales el sujeto modifica los recursos que asigna al procesamiento de cada ensayo. Se parte de la base de que estos mecanismos siguen patrones similares a los propuestos por el modelo del cerebro bayesiano (Friston, 2010).

Todo este análisis se lleva a cabo en base a los datos obtenidos en dos experimentos diferentes:

(i) en el primer experimento se establece en todos los bloques (100 ensayos por bloque) el mismo porcentaje de ensayos válidos (80%) e inválidos (20%). El objetivo es el estudio de las parejas de ensayos (combinando las condiciones válido e inválido) de forma que se puedan detectar las posibles diferencias entre ensayos en función de la condición por la que hayan sido precedidos.

(ii) En el segundo experimento se establecen 3 tipos de bloques de ensayos (bloque 1: 50% de ensayos válidos e inválidos / bloque 2: 68% de ensayos válidos y 32% de ensayos inválidos / bloque 3: 86% de ensayos válidos y 14% de ensayos inválidos). En este caso, el objetivo es el estudio de las diferencias entre ensayos individuales, dentro de cada tipo de bloque.

> Hipótesis

Arjona, A., Gómez, C.M., 2011. Trial-by-trial changes in a priori informational value of external cues and subjective expectancies in human auditory attention. PLoS One 6 (6), e21033.

1. Los ensayos válidos precedidos por ensayos válidos (VV) presentarán tiempos de reacción más reducidos y mayor porcentaje de anticipaciones que los ensayos válidos precedidos por ensayos inválidos (IV). Esto es debido a que la validez del ensayo previo incrementa la credibilidad de la clave como predictora del lado en el que aparecerá el estímulo objetivo. De este modo, la preparación para responder en el lado indicado por la

clave será mayor.

2. Los ensayos inválidos precedidos por ensayos válidos (VI) presentarán tiempos de reacción mayores y mayor porcentaje de respuestas incorrectas que los ensayos inválidos precedidos por ensayos inválidos (II). Esto es debido a que la validez del ensayo previo incrementa la credibilidad de la clave como predictora del lado en el que aparecerá el estímulo objetivo. De este modo, la preparación para responder en el lado incorrecto será mayor en un ensayo inválido precedido por un ensayo válido, dando lugar a un mayor esfuerzo para redirigir los recursos atencionales del lado incorrecto al correcto.
3. Efecto de Alternancia-Repetición: Los ensayos precedidos por dos ensayos en los que el estímulo objetivo aparece en el mismo lado (ej. izquierda-izquierda-izquierda) tendrán tiempos de reacción más bajos que los ensayos precedidos por dos ensayos con estímulos objetivos en posiciones alternantes (ej. derecha-izquierda-izquierda).

Arjona, A., Escudero, M., Gómez, C.M., 2014. Updating of attentional and premotor allocation resources as function of previous trial outcome. Sci. Rep. 4, 4526.

4. La CNV será más negativa en los ensayos precedidos por ensayos válidos, en comparación con los ensayos precedidos por ensayos inválidos. Esta negatividad reflejaría la mayor preparación atencional para responder en el lado indicado por la clave.
5. La LRP presentará una mayor positividad en los ensayos precedidos por ensayos válidos en comparación con los ensayos precedidos por ensayos inválidos. Este potencial indicaría la mayor preparación motora para responder en el lado indicado por la clave.

Arjona, A., Gómez, J., Gómez, C.M., 2017. Event related potentials changes associated with the processing of auditory valid and invalid targets as a function of

previous trial validity in a Posner's paradigm. Neurosci Res, 115, 37-43.

6. Los ensayos válidos precedidos por ensayos inválidos (IV) presentaran una Processing Negativity de mayor amplitud, en comparación con los ensayos válidos precedidos por ensayos válidos (VV). Esta diferencia sería ocasionada por el mayor esfuerzo de orientación atencional (hacia el estímulo objetivo) requerido en los ensayos válidos precedidos por ensayos inválidos, donde la credibilidad de la clave es más baja y, por tanto, la preparación para responder en el lado indicado, también es menor.
7. Igualmente, en los ensayos inválidos precedidos por ensayos válidos (VI) aparecerá una Processing Negativity de mayor amplitud, en comparación con los ensayos inválidos precedidos por ensayos inválidos (II). Esto sería debido al mayor esfuerzo atencional requerido para responder a un ensayo inválido cuando la credibilidad de la clave es mayor porque viene precedido por un ensayo válido. En cambio, cuando un ensayo inválido es precedido por otro ensayo inválido, el sujeto estaría prestando menos atención a la posición señalizada por la clave y necesitaría un menor esfuerzo para reorientarse hacia el lado no previsto.
8. Los ensayos válidos precedidos por ensayos inválidos (IV) mostrarán un incremento de los potenciales P3a y P3b, en comparación con los ensayos válidos precedidos por ensayos válidos (VV). Esto es debido a que tras un ensayo inválido, el ensayo válido es menos esperado y requiere un mayor procesamiento y actualización de la credibilidad asignada a la clave.
9. Del mismo modo, los ensayos inválidos precedidos por ensayos válidos (VI) mostrarán un incremento de los potenciales P3a y P3b, en comparación con los ensayos inválidos precedidos por ensayos inválidos (II). En las secuencias II el sujeto realizará predicciones de menor intensidad que en las secuencias VI, por lo que necesitará una menor

actualización de la credibilidad de la clave una vez llegado el estímulo objetivo incorrectamente señalizado.

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10. La amplitud de la CNV será mayor a medida que la proporción de ensayos válidos por bloque aumente (50%-68%-86%). Este crecimiento de la CNV sería debido a que la preparación atencional generada por la clave es mayor al haber más ensayos válidos.
11. La amplitud de los componentes N1 y P2a (tras el estímulo objetivo) será mayor en los ensayos válidos, en comparación con los ensayos inválidos, a medida que aumente la proporción de ensayos válidos en el bloque (50%-68%-86%). Este proceso reflejaría la mayor modulación atencional generada tras la aparición del estímulo objetivo en el lado esperado.
12. Como posible alternativa a la anterior, los componentes N1 y P2 no presentarán un incremento de amplitud en los ensayos válidos, en comparación con los ensayos inválidos, a medida que aumente la proporción de ensayos válidos en el bloque. Esto sería debido al efecto opuesto generado por los procesos de atención y predicción.
13. La amplitud de los componentes P2p, P3a y P3b será mayor en los ensayos inválidos, en comparación con los ensayos válidos, a medida que aumente la proporción de ensayos válidos por bloque (50%-68%-86%). Esta diferencia reflejaría el mayor esfuerzo de reorientación atencional y actualización de la memoria de trabajo generado por un estímulo target más inesperado al ser menos frecuentes los ensayos inválidos.
14. En base a la idea de que la amplitud de la CNV indica la preparación para responder generada por la clave, y el componente P3b refleja la evaluación del posible error

cometido en la predicción del lugar donde aparece el target, así como la actualización de la credibilidad asignada a la clave; la modulación de ambos componentes presentará una correlación significativa, consecuencia de la relación entre los procesos que representan.

15. La Negative Slow Wave mostrará una mayor diferencia entre los ensayos válidos e inválidos, a medida que aumente la proporción de ensayos válidos por bloque (50%-68%-86%). Esta modulación será consecuencia de la mayor demanda atencional necesaria para reorientar la atención y/o el mayor estado de alerta que se genera tras un inesperado ensayo inválido.

- Resultados

Arjona, A., Gómez, C.M., 2011. Trial-by-trial changes in a priori informational value of external cues and subjective expectancies in human auditory attention. PLoS One 6 (6), e21033.

- ✓ Se observó una reducción significativa de los Tiempos de Reacción (RTs), así como un aumento del porcentaje de Anticipaciones y una reducción de las respuestas incorrectas, en función de que los ensayos fuesen válidos y estuviesen precedidos por uno o incluso dos ensayos válidos.
- ✓ Los ensayos inválidos precedidos por ensayos válidos (VI) mostraron un coste mayor en los RTs, así como un menor número de anticipaciones y un mayor porcentaje de respuestas incorrectas, en comparación con los ensayos inválidos precedidos por ensayos inválidos (II).
- ✓ Los patrones de crecimiento entre las anticipaciones y las respuestas incorrectas fueron opuestos; mientras que las secuencias terminadas en ensayos válidos (VV, IV)

presentaron un mayor número de anticipaciones y una reducción de las Respuestas Incorrectas, las secuencias terminadas en ensayos inválidos (II, VI) mostraron una mayor cantidad de Respuestas Incorrectas y un menor porcentaje de Anticipaciones.

- ✓ La media de los RTs, así como el porcentaje de respuestas incorrectas, mostraron una reducción en los ensayos precedidos por ensayos en los que el estímulo target había aparecido en el lado opuesto, en comparación con los ensayos en los que el target aparecía en el mismo lado que en el ensayo anterior (efecto de alternancia de primer orden). Además, los RTs también mostraron una reducción significativa en ensayos precedidos por dos alternancias en el lugar de aparición del target (ej. izquierda-derecha-izquierda), en comparación con los ensayos precedidos por una repetición y una alternancia (ej. derecha-derecha-izquierda). Igualmente, los ensayos precedidos por dos repeticiones (ej. derecha-derecha-derecha) mostraron RTs más reducidos que los precedidos por una alternancia y una repetición (ej. izquierda-derecha-derecha).

Arjona, A., Escudero, M., Gómez, C.M., 2014. Updating of attentional and premotor allocation resources as function of previous trial outcome. Sci. Rep. 4, 4526.

- ✓ La CNV (Contingent Negative Variation) mostró un aumento significativo de amplitud en los ensayos precedidos por ensayos válidos, en comparación con los ensayos precedidos por ensayos inválidos, reflejando una ajuste dinámico (ensayo a ensayo) de los recursos atencionales.
- ✓ La LRP (Lateralized Readiness Potential) mostró igualmente una mayor amplitud en los ensayos precedidos por ensayos válidos, en comparación con los ensayos precedidos por ensayos inválidos, indicando una mayor preparación motora para responder tras confirmar la expectativa creada por la clave en el ensayo previo.

- ✓ La EDAN (Early Directing Attention Negativity) mostró ausencia de influencia generada por la condición del ensayo previo, lo cual indicaría que el efecto de validez/invalidez entre ensayos no es debido a una modulación temprana de la atención prestada a la clave.

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- ✓ Los resultados mostraron un aumento de la amplitud del componente N1 auditivo, tras la aparición del estímulo S2, en los ensayos válidos precedidos por ensayos inválidos (IV), en comparación con los ensayos válidos precedidos por ensayos válidos (VV). En contraste, el componente P2 mostró un aumento de amplitud en los ensayos válidos precedidos por ensayos válidos (VV), en comparación con los ensayos válidos precedidos por ensayos inválidos (IV). Ambos componentes estarían afectados por la PN (Processing Negativity), que al superponerse sobre ellos incrementa el N1 y disminuye el P2 en los ensayos válidos precedidos por ensayos inválidos (IV).
- ✓ Los componentes P3a y P3b mostraron una positividad mayor en los ensayos inválidos precedidos por ensayos válidos (VI), en comparación con los ensayos inválidos precedidos por ensayos inválidos (II), indicando una mayor reorientación atencional (P3a) y actualización de la memoria de trabajo (P3b) tras un ensayo inválido precedido por un ensayo válido.

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- ✓ El efecto de la clave sobre los RTs (RTs más reducidos en los ensayos válidos, en comparación con los ensayos inválidos) fue mayor a medida que aumentaba la proporción de ensayos válidos por bloque (50%<68%<86%), indicando una mayor preparación sensorial/motora generada por la clave cuanto mayor es la cantidad de ensayos válidos por bloque y viceversa.
- ✓ El porcentaje de respuestas incorrectas en los ensayos inválidos, en comparación con los ensayos válidos, fue incrementando a medida que aumentaba la proporción de ensayos válidos por bloque. Esto indicó una mayor tendencia a emitir respuestas incorrectas de manera impulsiva a medida que el número de ensayos válidos aumentaba.
- ✓ El cambio en la proporción de ensayos válidos por bloque no provocó diferencias significativas en la modulación de la CNV, debido posiblemente a que el escaso período transcurrido entre la clave y el sonido (360 ms) no permitía generar una CNV completa.
- ✓ El componente lateralizado de la CNV mostró un incremento de amplitud en los bloques con un 86% de ensayos válidos, en comparación con los bloques con un 50% de ensayos válidos. Este incremento de amplitud indicaría una mayor preparación para responder (sensorial y motora), en el hemisferio contralateral al lado indicado por la clave, a medida que aumenta el porcentaje de ensayos válidos en el bloque.
- ✓ El componente N1 auditivo, aparecido tras el estímulo S2, no mostró una modulación significativa generada por la interacción entre el efecto de la condición del ensayo (válido/inválido) y el efecto del porcentaje de validez del bloque (50%, 68%, 86%).
- ✓ El componente P2a mostró una mayor amplitud en los ensayos válidos, en comparación con los ensayos inválidos, siendo mayor esta diferencia en los bloques con 86% y 68% de ensayos válidos, comparados con el bloque de 50%. Esta diferencia reflejaría un mayor procesamiento atencional pos-target en los ensayos válidos a medida que aumenta el porcentaje de los mismos.

- ✓ El componente P2p fue más positivo en los ensayos inválidos, en comparación con los ensayos válidos. Sin embargo, no hubo diferencias significativas entre los bloques en relación con la condición.
- ✓ Los componentes P3a y P3b presentaron una mayor amplitud en los ensayos inválidos, en comparación con los válidos, pero sólo el P3b mostró una mayor diferencia entre condiciones a medida que aumentaba la proporción de ensayos válidos por bloque. Este incremento del P3b sugeriría una mayor actualización de la memoria de trabajo en los ensayos inválidos a medida que éstos son más inesperados.
- ✓ La NSW (Negative Slow Wave) mostró una mayor diferenciación entre condiciones (válida e inválida) a medida que aumentaba la proporción de ensayos válidos por bloque.

- Discusión

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Los resultados obtenidos en el presente experimento con respecto a los RTs corroboran el efecto clásico del coste y el beneficio que se produce en el PCCP (Posner, 1980). De este modo, las secuencias de dos ensayos terminadas en un ensayo válido (V) (válido-válido (VV) / inválido-válido (IV)) mostraron una reducción de los RTs, en comparación con las secuencias terminadas en un ensayo inválido (I) (inválido-inválido (II)/ válido-inválido (VI)). Este efecto sería debido a que la clave (flecha) activa la corteza sensorial, motora y premotora del hemisferio opuesto al lado indicado, lo cual facilitaría tanto la percepción del estímulo como la generación anticipada de la respuesta

correcta en los ensayos válidos (Mangun y col., 1991; Hopfinger y col., 2000; Gómez y col., 2004; Flores y col., 2009). En este sentido, el funcionamiento del sistema atencional en el PCCP sería semejante a la llamada inferencia Bayesiana (Friston, 2009), de modo que el sujeto durante la tarea estaría haciendo predicciones sobre la posible futura localización del estímulo target y pre-activando las áreas cerebrales necesarias para emitir la respuesta. Esta teoría explicaría no sólo el beneficio de los RTs en los ensayos válidos, sino también el coste en los ensayos inválidos, debido al proceso de reorientación de la red atencional. Éstas ideas encajarían además con el llamado Modelo de competencia sesgada (Desimone y col., 1995; Gómez y col., 1995), dado que el ejecutivo central se encargaría de seleccionar y activar la corteza sensorial necesaria para percibir el estímulo esperado con mayor facilidad. La red fronto-parietal dorsolateral activaría la corteza sensorial a través de inputs neurales para ganar esa ventaja en el procesamiento del estímulo en la posición indicada (Corbetta y col., 2008). En el caso de los ensayos inválidos, el giro frontal inferior sería una de las áreas implicadas en el procesamiento la novedad del estímulo inesperado (Corbetta y col., 2008; Vossel y col., 2006).

Por otro lado, diferentes resultados corroboran el conocido como efecto secuencial de validez/invalidez (Jongen y Smulders, 2007; Gómez y col., 2009). Los ensayos válidos precedidos por uno o dos ensayos válidos (VV y VVV) mostraron tanto una reducción del RTs como un aumento claro de las anticipaciones (indicando la tendencia a responder incluso antes de haber procesado el target). Las secuencias de dos ensayos mostraron un patrón claro de crecimiento de los RTs (VV<IV<II<VI). El aumento de los RTs en los ensayos inválidos precedidos por un ensayo válido (VI) con respecto a los ensayos inválidos precedidos por uno inválido (II) confirmaría especialmente la idea de la preparación atencional previa generando un coste a la hora de responder a un ensayo

inválido (Hopfinger y col., 2000; Gómez y col., 2004; Flores y col., 2009). De este modo, la clave de un ensayo inválido precedido por otro inválido generaría una preparación menor para responder al lado indicado, en comparación con la clave de un ensayo inválido precedido por uno válido (en este caso su credibilidad es mayor). En el caso de las triadas de ensayos, también se observo un patrón de crecimiento de los RTs que confirmaría el cambio en la atención prestada a la clave en función de lo ocurrido en los dos ensayos previos (VVV<IVV<IIV).

En el caso de los errores, lo más destacable fue el patrón inverso entre las respuestas incorrectas (con un porcentaje alto en las secuencias VI y bajo en VV) y las anticipaciones (la mayoría en las secuencias VV y un porcentaje muy bajo en VI). Las respuestas incorrectas mostraron un promedio de RTs bastante rápido, lo cual indica que el fallo era debido en la mayoría de las ocasiones a la anticipación a la hora de responder. Este proceso de antelación a la hora de responder (que da lugar tanto a las anticipaciones como las respuestas incorrectas) se podría entender como la consecuencia de una interacción entre la información endógena (que incita a responder a un lado) y la exógena (que proviene del estímulo target) (Delinte y col., 2002). En el caso de las anticipaciones se produce una congruencia entre ambas informaciones, pero en el caso de las respuestas incorrectas la información endógena termina induciendo al error antes de procesar correctamente el estímulo target.

El patrón obtenido en el presente experimento con respecto a los RTs sugiere que la información se va transfiriendo de un ensayo a otro. De este modo, la confirmación o no de la expectativa generada por la clave en un ensayo influye en el nivel de atención generado por la clave en el siguiente ensayo. Esta idea estaría relacionada con la

propuesta de Yu y Dayan (2005) en su análisis del patrón de coste-beneficio, donde destacan el balance entre la influencia de la información sensorial (bottom-up) y las ideas a priori (top-down). En este sentido, destacaron el PCCP como un buen modelo para estudiar el aprendizaje bayesiano de las probabilidades; los ensayos inválidos provocarían que el sujeto preste menos atención a la información previa (top-down) y más a la sensorial (bottom-up), mientras que los válidos generarían el efecto opuesto. Por otro lado, se ha reportado que la atención puede ser entendida puramente en términos de optimización de la precisión o la credibilidad de las representaciones (Friston, 2010). Por todo ello, el aumento de los RTs en los ensayos válidos precedidos por ensayos inválidos (IV), en comparación con los ensayos válidos precedidos por ensayos válidos (VV), así como en VI con respecto a II, sería consecuencia de la existencia de un proceso continuado (ensayo a ensayo) de actualización del valor predictivo de la clave espacial. La misma idea sería aplicable a los resultados obtenidos en los RTs con respecto a las triadas de ensayos VVV<IVV.

El concepto de inferencia Bayesiana propuesto por Friston (2009) computaría la validez de la predicción hecha en cada ensayo como el 'error de predicción', y la credibilidad de la clave como predictora del target se calcularía o reevaluaría ensayo a ensayo. En esta línea, tanto los resultados obtenidos en el presente estudio con respecto a los RTs y los errores, como los resultados reportados por Jongen y Smulders (2007) sobre los RTs, encajarían con dicha inferencia Bayesiana. Por otro lado, el PCCP también sería un buen modelo para evaluar el conocido como ciclo cognitivo de adaptación al ambiente (Gómez y Flores, 2011; Fuster, 2004), basado en la preparación, la emisión de una respuesta, la evaluación del resultado, y la transferencia de información al ensayo siguiente.

Una explicación alternativa a las propuestas hasta ahora, con respecto al efecto secuencial de validez/invalidez, plantea un aumento del control cognitivo (y en consecuencia de los RTs) en los ensayos válidos precedidos por ensayos inválidos (IV), en comparación con los ensayos válidos precedidos por ensayos válidos (VV) (Botvinick y col., 2001/2004). Sin embargo, en base a este enfoque, el aumento de los RTs en las secuencias VI con respecto a II (reportado en varias ocasiones (Jongen y Smulders, 2007; Gómez y col., 2008)) debería ser una disminución provocada por un mayor control cognitivo tras un ensayo inválido. En este sentido, la razón puede estar en el hecho de que los experimentos en los que se ha usado la teoría del control cognitivo para explicar los RTs usaban tareas con tiempos de demora más cortos y sin clave entre los estímulos (Gratton y col., 1992; Stürmer y col., 2002; Notebaert y col., 2006).

Con respecto al efecto de alternancia (Bertelson y col., 1966), los ensayos precedidos por ensayos en los que el estímulo target apareció en el lado opuesto (ej.: izquierda-derecha) mostraron un beneficio en los RTs. Sin embargo, este efecto no mostró interacción con el de la validez de la clave, indicando que es independiente a si el ensayo es válido o inválido. El hecho de que se produzca un efecto secuencial de alternancia indicaría que el sujeto puede estar siguiendo una regla similar a la conocida 'falacia del jugador', de modo que tiende a pensar que si algo ocurre en un ensayo (en este caso el target aparece en un lado), es menos probable que ocurra en el ensayo siguiente. En el caso de la presente tarea, los sujetos tenderían a pensar que si el estímulo target de un ensayo (n) aparece a la derecha, en el ensayo siguiente (n+1) aparecerá a la izquierda, y viceversa. Según estudios previos basado en el análisis de la LRP (Lateralized Readiness Potential), sería un efecto provocado por la preparación motora para responder a un lado

(Leuthold y col., 1993; Gómez y col., 2005).

Arjona, A., Escudero, M., Gómez, C.M., 2014. Updating of attentional and premotor allocation resources as function of previous trial outcome. Sci. Rep. 4, 4526.

Los resultados sobre potenciales pre-target obtenidos en el presente estudio sugieren que la atención prestada a las claves espaciales va modulándose continuamente en base a lo ocurrido en el ensayo previo. El PCCP permite analizar la distribución de los recursos atencionales, así como la preparación para responder al estímulo target, ensayo a ensayo. La validez o invalidez del ensayo previo aumenta o disminuye la capacidad de la clave para orientar al sujeto a percibir el target y responder en uno de los dos lados.

Estudios previos sobre el efecto de validez/invalidez en el PCCP han demostrado que los sujetos responden con mayor rapidez en los ensayos válidos (Posner, 1980). Igualmente, estudios más recientes sobre el efecto de validez/invalidez entre ensayos han reportado la influencia del resultado del ensayo previo sobre la realización del siguiente (Gómez y col., 2009; Jongen y Smulders, 2007). El presente experimento replicaría estos últimos resultados. La explicación a este efecto sería que la validez de la clave en un ensayo (n) incrementaría la credibilidad de la misma en el siguiente ensayo (n+1), generando una mayor orientación atencional para responder al target antes de que aparezca. Esto se refleja finalmente en unos tiempos de reacción más cortos en los ensayos válidos precedidos por ensayos válidos (VV), en comparación con los ensayos válidos precedidos por ensayos inválidos (IV). En otras palabras, la probabilidad condicional de una combinación válida 'clave-target' se vería incrementada tras un ensayo válido. Por otro lado, cabe destacar que los ensayos inválidos precedidos por

ensayos inválidos (II) presentaron RTs más reducidos que los ensayos inválidos precedidos por ensayos válidos (VI). En este caso, la explicación sería que los sujetos prestan menos atención a una clave inválida si viene precedida por un ensayo inválido, por lo que les cuesta menos rectificar o redireccionar sus recursos atencionales de un lado al otro. Por último, las anticipaciones y respuestas incorrectas muestran porcentajes consistentes con la teoría de la preparación atencional y motora. En ambos casos la validez previa generaría una mayor actividad top-down, induciendo un mayor número de anticipaciones en los ensayos válidos y un mayor número de respuestas incorrectas en los ensayos inválidos.

Adicionalmente, los resultados mostraron que no hubo una influencia del ensayo previo basada en el cambio de la dirección de la clave, o de la localización del target. Este dato sugiere que el conocido como 'binding effect' (que se referiría, en este caso, a la influencia generada por el hecho de repetir o no la misma combinación cue-target) no tiene relación con el efecto de la validez de la clave en el PCCP (Verguts, 2009).

Desde el punto de vista de los estudios neuropsicológicos, se ha reportado que durante el periodo de demora entre la clave y el target se produce una activación de las zonas frontales relacionada con el mantenimiento de la atención. Por otro lado, la preparación para emitir la respuesta manual, genera un aumento de actividad en áreas sensoriales y motoras contralaterales al lado indicado por la clave (Gómez y col., 2004; Flores y col., 2009; Gómez y Flores, 2011; Hopfinger y col., 2000). Estos resultados serían consistentes con el llamado 'Biased Competition Model' (Desimone y Duncan, 1995), el cual establece un mecanismo que permite al sujeto procesar más fácilmente los ítems relevantes. De este modo, el sistema atencional pre-activaría la corteza auditiva y

motora del lado contralateral al indicado por la clave, facilitando la percepción del sonido y la emisión de una respuesta rápida (y correcta en el caso de los ensayos válidos) (Gómez y col., 2004). Esta pre-activación en cada ensayo (n) estaría basada en la asociación clave-target del ensayo previo (n-1). Tras un ensayo válido la asociación saldría fortalecida y en el ensayo siguiente la preparación para responder generada por la clave sería mayor (Gómez y Flores, 2011).

Los resultados obtenidos en el EEG con respecto a la EDAN mostraron que este componente no es modulado por la condición del ensayo previo. Este dato indicaría que el efecto de validez/invalidez entre ensayos no es consecuencia de un sesgo atencional temprano, es decir, que la atención a la clave (representada por la EDAN) se mantiene independientemente de la condición del ensayo previo, por lo que la mayor o menor preparación para responder al target (representada por la amplitud de los componentes CNV y LRP) sería generada únicamente por la credibilidad asignada a la clave en cada ensayo.

A diferencia de la EDAN, la amplitud de la CNV varió significativamente en función de la condición del ensayo previo. Este efecto, junto con el de los RTs, corroboran la idea de que la atención se modula ensayo a ensayo en base a la condición previa (Arjona y Gómez, 2014a). El efecto de validez/invalidez entre ensayos generó una CNV más negativa en los ensayos precedidos por ensayos válidos, en comparación con los ensayos precedidos por ensayos inválidos, el cual se interpretaría como un aumento de la expectación/preparación generada por la clave tras un ensayo válido. Teniendo en cuenta que la CNV se ha asociado con activación de redes frontoparietales (Gómez y col., 2007) y de áreas sensoriales y motoras específicas de la tarea (Gómez y col., 2004; Flores y col.,

2009), cabría asumir que la validez previa de la clave induce una activación elevada de estas redes.

Por su parte, la LRP fue medida en electrodos fronto-centrales (F3/F4, FC3/FC4, C3/C4), mostrado, al igual que la CNV, un incremento de amplitud en los ensayos precedidos por ensayos válidos, en comparación con los ensayos precedidos por ensayos inválidos. Este resultado indicaría una mayor preparación motora para responder al target en el lado indicado por la clave tras un ensayo válido (Kutas y Donchin, 1980). Además, sería consistente con el beneficio observado en los RTs para los ensayos válidos precedidos por ensayos válidos (VV<IV), así como para los ensayos inválidos precedidos por ensayos inválidos (II<VI). En este último caso, la invalidez del ensayo previo generaría una menor preparación motora para responder en el ensayo siguiente, por lo que el retraso en la respuesta generado por la invalidez de la clave sería menor.

Hay que mencionar que actualmente no está aclarada la idea de si la LRP se corresponde con la fase tardía de la CNV, o ambos componentes reflejan procesos diferentes (Rohrbaugh y col., 1983; Van Boxtel y col., 1994). En el caso del presente estudio, al usar únicamente resultados de EEG, es difícil definir si la LRP, que sería una CNV lateralizada, es consecuencia de procesos de preparación sensoriales, motores, o de ambos. En cualquier caso, la influencia de la condición del ensayo previo en la amplitud tanto de la CNV, como de la LRP, indica una actualización ensayo a ensayo de la credibilidad de la clave, lo cual se refleja en el patrón obtenido en los RTs (VV<IV<II<VI).

Arjona, A., Gómez, J., Gómez, C.M., 2017. Event related potentials changes

associated with the processing of auditory valid and invalid targets as a function of previous trial validity in a Posner's paradigm. Neurosci Res, 115, 37-43.

Los resultados mostraron que el componente N1 auditivo post-target (S2) presenta una mayor amplitud en los ensayos válidos precedidos por un ensayo inválido (IV), en comparación con los ensayos válidos precedidos por un ensayo válido (VV). En este sentido, estudios sobre el N1 (Summerfield y de Lange, 2014) han reportado una disminución de la amplitud de este componente cuanto más predecible es la llegada del target. Por tanto, el aumento de N1 en las secuencias IV puede ser consecuencia de la menor predictibilidad del ensayo válido tras uno inválido. Por su parte, el componente P2 presentó una mayor amplitud en las secuencias VV, en comparación con las secuencias IV. En base a la teoría de la Processing Negativity (PN) (Michie y col., 1990; Näätänen y Michie, 1979), ambos componentes (N1 y P2) estarían igualmente afectados por esta negatividad que se superpone y aumenta la amplitud del N1, pero disminuye la del P2, en los ensayos válidos precedidos por ensayos inválidos (IV), en comparación con los ensayos válidos precedidos por ensayos válidos (VV). La PN ha sido reportada como una negatividad que se relaciona con el esfuerzo atencional, de modo que, en el caso de los ensayos válidos precedidos por ensayos inválidos, el sujeto realizaría un mayor esfuerzo atencional para procesar la validez, ya que es más inesperada. En otras palabras, el incremento de la PN en los ensayos válidos precedidos por ensayos inválidos vendría originado por la menor preparación atencional y motora (CNV y LRP de menor amplitud) que tiene lugar tras un ensayo inválido. La falta de credibilidad de la clave tras un ensayo inválido, daría lugar a un mayor esfuerzo atencional para procesar el siguiente target válido.

Con respecto a los componentes P3a y P3b, los resultados obtenidos añaden evidencia a la idea de que estos potenciales se relacionan con los procesos de análisis del error de predicción: la diferencia entre lo que se esperaba y lo que realmente ocurre (Kolossa y col., 2015; Seer y col., 2016). Concretamente, los análisis mostraron que ambos componentes presentan una mayor positividad en los ensayos inválidos precedidos por ensayos válidos (VI), en comparación con los ensayos inválidos precedidos por ensayos inválidos (II). Este resultado indicaría que el estímulo target inválido es más inesperado tras un ensayo válido, lo que podría interpretarse como el origen de un mayor proceso de reorientación atencional (P3a), así como de una mayor actualización de la memoria de trabajo (P3b) (Gómez y Flores, 2011; Mangun y Hillyard, 1991; Eimer, 1993; Gómez y col., 2008). Este proceso de actualización de la memoria de trabajo puede tener su origen en la incongruencia de la información aportada por la clave, y permitiría reevaluar la credibilidad de la misma. En suma, el cambio de validez de la clave (en este caso de válida a inválida) provoca que la invalidez sea más inesperada, y requiera un mayor análisis de error y una mayor actualización de la credibilidad de la relación clave-target. Cabe reseñar que, a pesar de que se han reportado ciertos efectos marginales al comparar las secuencias IV frente a VV en la modalidad visual (Gómez y col., 2009), en el presente análisis no se han detectado diferencias con respecto al P3a o P3b. En base a este dato, se podría entender los ensayos inválidos, en comparación con los válidos, generan por si solos un mayor procesamiento cerebral y, por tanto, una mayor amplitud de los componentes P3a y P3b (Gómez y Flores, 2011; Mangun y Hillyard, 1991)

Arjona, A., Gómez, C.M., 2016. Cue validity probability influences neural processing of targets. Biol. Psychol. 119, 171–183.

Esta nueva versión del PCCP (basada en la combinación de diferentes porcentajes de ensayos válidos/inválidos por bloque) se diseñó con el fin de analizar, con un nivel mayor de especificidad, el proceso de modulación dinámica de los potenciales cognitivos relacionados con la predicción y la preparación para responder a los eventos próximos. En este estudio se analiza la combinación de dos efectos; (i) el clásico efecto de validez/invalidez de la clave (Arjona y col., 2011/2014a/2014b; Jongen y Smulders, 2007); y (ii) el posible efecto generado por el porcentaje de validez del bloque de ensayos (50%, 68% y 86%). Los parámetros conductuales analizados son los Tiempos de Reacción (RTs), las Anticipaciones y las Respuestas Incorrectas. Mientras que, a nivel neural, se estudian las posibles modulaciones de la Contingent Negative Variation (CNV), así como los componentes pos-target inducidos por el estímulo auditivo (N1, P2a, P2p, P3a, P3b y la Negative Slow Wave (NSW)). En conjunto, los resultados conductuales y neurales corroboraron los efectos de validez/invalidez de la clave y, además, mostraron una interacción significativa entre el porcentaje de validez del bloque (50%, 68% y 86%) y la condición del ensayo (válido/inválido).

- *Resultados conductuales*

Diferentes estudios han reportado que el ratio de validez/invalidez de la clave, en un bloque de ensayos, tiene una influencia significativa sobre el efecto de validez de la clave (Jonides, 1983; Riggio y Kirsner, 1997; Vossel y col., 2014). Los resultados de los RTs en el presente estudio muestran que existe una interacción significativa entre el efecto de validez/invalidez de la clave y la proporción de ensayos válidos por bloque; a medida que aumenta la proporción de ensayos válidos por bloque (50%-68%-86%) la diferencia entre los RTs de los ensayos válidos e inválidos se hace más grande. Una

posible explicación de este efecto, sería que el incremento del porcentaje de ensayos válidos, aumenta la credibilidad de la clave, y, con ello, la pre-activación de las áreas sensorio-motoras generada por la misma. La orientación para percibir el target y emitir una respuesta en el lado indicado por la clave sería más fuerte cuanto mayor es el porcentaje de ensayos válidos por bloque. Esta mayor preparación desembocaría en una reducción de los RTs en los ensayos válidos, y un aumento en los ensayos inválidos. En base al modelo Bayesiano (Feldman y Friston, 2010) la idea sería que la probabilidad condicional de que aparezca una combinación clave-target válida (p (S2/S1)), aumenta a medida que se incrementa la proporción de ensayos válidos por bloque. Por otro lado, la diferencia entre el porcentaje de Respuestas incorrectas en los ensayos válidos e inválidos, también creció a medida que aumentaba la proporción de ensayos válidos por bloque. Este resultado iría en consonancia con el aumento de la credibilidad de la clave, y, con ello, de la preparación para responder erróneamente en los ensayos inválidos.

- *Resultados de los Potenciales Relacionados con Eventos*

- *CNV*

La CNV fue analizada en sus electrodos centrales mediante la comparación de la modulación generada por las claves válidas e inválidas en los 3 tipos de bloques de ensayos (50%, 68% y 86%). Desde este punto de vista, los resultados no mostraron una modulación significativa de la CNV generada por el cambio en el porcentaje de validez del bloque. Una razón posible para esta ausencia de efecto es la escasa duración del periodo entre la clave y el target (360 ms), que impidió la generación de una onda lenta más pronunciada (reflejando una mayor expectación por la llegada del target). En este

sentido, Scheibe y col. (2009), en un experimento parecido, pero con un periodo de 2 segundos entre la clave y el target, mostraron que la CNV se modulaba de acuerdo con la probabilidad a priori de aparición del target.

- *CNV lateralizada*

Por su parte, la llamada CNV lateralizada (analizada en parejas de electrodos laterales) mostró un aumento significativo en el bloque de 86%, en comparación con el bloque de 50%. Este resultado indicaría una mayor preparación (posiblemente no sólo motora, sino también sensorial) para emitir una respuesta en el lado indicado por la clave, cuando la proporción de ensayos válidos es mayor. El aumento de activación se produciría en el hemisferio contralateral a la mano que se prepara para responder. En este sentido, un experimento similar, pero usando Magnetoencefalografía, mostró que durante el período de la CNV, se activaba no solamente la corteza motora, si no también la corteza auditiva contralateral al lado indicado por la clave (Gómez y col., 2004). Una posible explicación para este incremento en la amplitud de la CNV lateralizada en el bloque de 86%, sería que representa un incremento de la actividad basal del cerebro. En esta línea, Summerfield y de Lange (2014) propusieron que los cambios en la actividad basal son un mecanismo para procesar cambios en las probabilidades a priori. De este modo, la CNV lateralizada indicaría esos cambios debidos a un flujo continuo de carga positiva en las dendritas apicales de las neuronas piramidales, produciendo una modulación del umbral de respuesta de las neuronas (Rockstroh y col., 1982).

- *Componentes pos-target auditivos N1 y P2a*

Los resultados obtenidos mediante ANOVAs sobre el componente N1 mostraron, en conjunto, una interacción significativa entre la condición y el bloque (diferencia entre condiciones en los diferentes bloques). Sin embargo, la aplicación de la corrección de Bonferroni a esta interacción no mostró diferencias concretas significativas. La causa más probable de esta ausencia de efecto en N1 sería la existencia de una superposición opuesta de procesos atencionales y predictivos (Summerfield y de Lange , 2014). En este sentido, Todorovic y col. (2011/2012), en una tarea con dos tonos, encontraron que cuanto más predecible es el estímulo más se reduce la amplitud de un componente relacionado con la latencia de N1. En suma, las tendencias opuestas generadas por los efectos atencionales (incremento de N1 en los ensayos válidos) y predictores (reducción de N1 en los ensayos válidos), darían lugar a una modulación del componente N1 demasiado reducida como para presentar diferencias significativas entre bloques.

En el caso del componente P2a (relacionado con mecanismos frontales reguladores de la atención selectiva (Potts y col., 1998)), se observó un incremento de amplitud en los ensayos válidos (relacionándose con un incremento de atención en estos ensayos), y una mayor diferencia entre condiciones en los bloques de 86% y 68%, en comparación con el bloque de 50%. Estudios previos han reportado que la amplitud del componente P2a no varía en función de la modalidad de presentación del estímulo target, o de la respuesta requerida en la tarea, lo que sugiere que estaría más relacionado con la relevancia o la atención prestada al estímulo (Potts y col., 1998; Potts y Tucker, 2001; Potts, 2004; Potts y col., 2004). Además, este componente frontal sería bastante similar a la llamada 'Frontal Selection Positivity (FSP)' (Kenemas y col., 1993; Makeig y col.,

1999; Potts, 2004), relacionada con el proceso de selección de las características relevantes del estímulo y la respuesta a emitir. En suma, el P2a podría considerarse un componente atencional relacionado con el proceso de discriminación del estímulo target, necesario para emitir una respuesta.

- *Componentes P2p, P3a y P3b*

El componente P2p (en su modalidad visual) ha sido asociado en diferentes publicaciones con procesos de memoria (Taylor y col., 1990; Wolach y Pratt, 2001; Freunberger y col., 2007). En el presente estudio se analizó la modalidad auditiva de este componente (reportado en Arjona y col., 2014a), y los resultados mostraron una mayor positividad en los ensayos inválidos, en comparación con los ensayos válidos. Sin embargo, el análisis de la interacción con el tipo de bloque indicó que no había una modulación de esta diferencia entre condiciones, en base al porcentaje de validez por bloque. Con respecto al origen de la mayor positividad del P2p en los ensayos inválidos, dos hipótesis se plantean; (i) por un lado, puede tratarse de una inversión de polaridad en la latencia del componente P2, entre la zona anterior (P2a) y la posterior (P2p), generada por un incremento de activación en las áreas mediales, relacionadas con el análisis del conflicto (siendo mayor el conflicto en los ensayos inválidos que en los válidos) (Botvinick y col., 2004); (ii) por otro lado, el componente P2p podría estar relacionado con la codificación de la información sobre el estímulo target, por parte de la memoria de trabajo, la cual se activaría con más intensidad tras un target inesperado (ensayo inválido) para actualizar la nueva información (de este modo el P2p se consideraría como un estadio temprano del P3b). En base a la estructura jerárquica planteada por el modelo del cerebro Bayesiano (Friston, 2009), que plantea que las cortezas de orden inferior reciben

información de las cortezas de orden superior para actualizar las probabilidades a priori, la diferencia de amplitud entre condiciones (válidas e inválidas) en el P2p indicaría el proceso de actualización generado por cortezas de orden inferior en base al error de predicción.

Con respecto a los componentes P3a y P3b, las diferentes investigaciones han reportado que presentan una mayor amplitud en los ensayos inválidos, en comparación con los ensayos válidos, tanto en la modalidad visual como la auditiva (Mangun y Hillyard, 1991; Golob y col., 2002; Gómez y col., 2008; Digiacomo y col., 2008; Arjona y col., 2014a). En el presente estudio, aunque se corrobora la mayor amplitud en los ensayos inválidos, sólo el componente P3b mostró una mayor diferencia entre condiciones a medida que aumentaba el porcentaje de ensayos válidos por bloque.

El componente P3a estaría relacionado con el procesamiento de la novedad, de los estímulos novedosos o inesperados, e implicaría un cambio atencional (Escera y col., 1998; Friedman y col., 2001; Dien y col., 2003; Polich, 2007). De este modo, en el PCCP, el aumento de la amplitud de este componente en los ensayos inválidos reflejaría la reorientación atencional generada por la llegada de un estímulo target inesperado (Gómez y col., 2008). En este sentido, se ha reportado que tanto la frecuencia de presentación de los estímulos, como la expectación subjetiva creada en el sujeto, están relacionadas con la amplitud del P3a visual (Digiacomo y col., 2008; Gómez y col., 2008) y auditivo (Arjona y col., 2014a). En el caso del presente estudio, la mayor positividad del P3a en los ensayos inválidos de los 3 tipos de bloques (50%, 68% y 86%) reflejaría una fuerte tendencia a la reorientación atencional ante la sorpresa, independiente del ratio la validez/invalidez de los ensayos.

Por su parte, el componente P3b aumenta igualmente tras la presentación de un estímulo inesperado o infrecuente, y se diferencia del P3a por su latencia más tardía (alrededor de 400 ms tras la aparición del estímulo), así como por su topografía más posterior (Squires y col., 1976; Duncan-Johnson y Donchin, 1977, 1982; Arjona y col., 2014a). En el PCCP, este componente se ha relacionado con la actualización del valor de probabilidad asignado a la clave como predictora del estímulo objetivo (Gómez y Flores, 2011). En este sentido, el presente estudio mostró una mayor amplitud del P3b en los ensayos inválidos, en comparación con los válidos, a medida que aumentaba el porcentaje de ensayos válidos por bloque. Este efecto indicaría que en los ensayos inválidos se produce una actualización del valor de la clave como predictora del target, y que esta actualización tiene más intensidad en función de que el porcentaje de ensayos inválidos sea menor (ya que el target se hace más inesperado). En otras palabras, el aumento del P3b en los ensayos inválidos probablemente esté reflejando el proceso de 'actualización de la memoria de trabajo' que se lleva a cabo ensayo a ensayo con el objetivo de incluir la nueva información de lo ocurrido (Donchin y Coles, 1988; Sommer y col., 1998; Arjona y col., 2014a). Volviendo a la teoría del cerebro Bayesiano (Friston, 2009), este incremento del P3b en los ensayos inválidos se relacionaría con el procesamiento del llamado 'error de predicción', así como con la actualización de la probabilidad condicional (p(S2/S1)) entre la clave y el estímulo objetivo (Gómez y Flores, 2011). En esta línea, la correlación positiva que se produce entre la modulación de la CNV lateralizada en un ensayo (n) y del P3b en el ensayo previo (n-1), apoyaría la idea bayesiana del P3b como un componente asociado a la evaluación de la adecuación entre la predicción (CNV) y la localización del estímulo objetivo. La CNV se relacionaría con la activación neural de las áreas necesarias para el procesamiento del estímulo target en

un ensayo, y esta activación estaría basada en la probabilidad condicional asignada a la clave (p(S2/S1)) en el ensayo anterior (P3b del ensayo anterior) (Gómez y col., 2001; Chennu y col., 2013; Arjona y col., 2014b).

- *Negative Slow Wave (NSW)*

La conocida como Negative Slow Wave es una onda tardía que aparece en zonas anteriores con una latencia similar a la del componente P3b. Es por ello que algunos autores han propuesto que podría tratarse, particularmente en niños, del lado negativo de los dipolos positivos posteriores (Van Leeuwen y col., 1998; Flores y col., 2009). A pesar de ello, mediante un estudio sobre lesión en el córtex prefrontal dorsolateral, se ha reportado, en la modalidad auditiva, un origen únicamente frontal de la NSW (Lovstad y col., 2012). Por otro lado, esta negatividad frontal en la latencia del P3b también ha sido descrita, en la modalidad auditiva, como el reflejo del esfuerzo de reorientación ante estímulos distractores (Wetzel y Schröger, 2014), o como la respuesta de alerta y orientación (Rohrbaugh y col., 1979).

El presente estudio muestra una mayor diferenciación entre condiciones en la NSW, a medida que aumenta la proporción de ensayos válidos por bloque. En base a los estudios previos, se podría plantear que este efecto de bloque entre las condiciones indica un mayor estado de alerta o un mayor esfuerzo de reorientación cuando los ensayos inválidos son más improbables, ya que aumenta la sorpresa generada por el cambio de condición. A pesar de ello, la escasa investigación sobre este componente sólo permite plantear meras hipótesis especulativas.

- Conclusiones

Arjona, A., Gómez, C.M., 2011. Trial-by-trial changes in a priori informational value of external cues and subjective expectancies in human auditory attention. PLoS One 6 (6), e21033.

1. Los resultados obtenidos con respecto a los RTs corroboran el efecto clásico del coste/ beneficio que se produce en el PCCP (Posner, 1980), es decir, las secuencias de dos ensayos terminadas en un ensayo válido (V) (válido-válido (VV) / inválido-válido (IV)) muestran una reducción de los RTs, en comparación con las secuencias terminadas en un ensayo inválido (I) (inválido-inválido (II)/ válido-inválido (VI)). En este sentido, el funcionamiento del sistema atencional en el PCCP sería semejante a la llamada inferencia Bayesiana (Friston, 2009), de modo que el sujeto durante la tarea estaría haciendo predicciones sobre la posible futura localización del estímulo target y pre-activando las áreas cerebrales necesarias para emitir la respuesta
2. El patrón obtenido en el presente experimento con respecto a los RTs sugiere que la información se va transfiriendo de un ensayo a otro (efecto secuencial de validez/invalidez (Jongen y Smulders, 2007; Gómez y col., 2009)). De este modo, la confirmación o no de la expectativa generada por la clave en un ensayo influye en el nivel de atención generado por la clave en el siguiente ensayo. En otras palabras, el aumento de los RTs en los ensayos válidos precedidos por ensayos inválidos (IV), en comparación con los ensayos válidos precedidos por ensayos válidos (VV), así como en VI con respecto a II, sería consecuencia de la existencia de un proceso continuado (ensayo a ensayo) de actualización del valor predictivo de la clave espacial. La misma idea sería

aplicable a los resultados obtenidos en los RTs con respecto a las triadas de ensayos VVV<IVV.

3. En base al concepto de inferencia Bayesiana propuesto por Friston (2009) la validez de la predicción hecha en cada ensayo se computaría como el 'error de predicción', y la credibilidad de la clave como predictora del target se calcularía o reevaluaría ensayo a ensayo.
4. El hecho de que se produzca un efecto secuencial de alternancia (Bertelson y col., 1966) indica que posiblemente el sujeto está siguiendo una regla similar a la que genera la conocida como 'falacia del jugador'. De este modo, en el caso de la presente tarea, el sujeto tiende a pensar que si el estímulo target de un ensayo (n) aparece a la derecha, en el ensayo siguiente (n+1) aparecerá a la izquierda, y viceversa.

Arjona, A., Escudero, M., Gómez, C.M., 2014. Updating of attentional and premotor allocation resources as function of previous trial outcome. Sci. Rep. 4, 4526.

1. La atención prestada a las claves espaciales va modulándose continuamente en base a lo ocurrido en el ensayo previo. El PCCP permite analizar la distribución de los recursos atencionales, así como la preparación para responder al estímulo target, ensayo a ensayo. La validez o invalidez del ensayo previo aumenta o disminuye la capacidad de la clave para orientar al sujeto a percibir el target y responder en uno de los dos lados.
2. La validez de la clave en un ensayo (n) incrementaría la credibilidad de la misma en el siguiente ensayo (n+1), generando una mayor orientación atencional para responder al target antes de que aparezca.

3. Los sujetos prestan menos atención a una clave inválida si viene precedida por un ensayo inválido, por lo que les cuesta menos rectificar o redireccionar sus recursos atencionales de un lado al otro
4. La validez del ensayo previo generaría una mayor actividad top-down, induciendo un mayor número de anticipaciones en los ensayos válidos y un mayor número de respuestas incorrectas en los ensayos inválidos.
5. El conocido como 'binding effect' (que se referiría, en este caso, a la influencia generada por el hecho de repetir o no la misma combinación cue-target) no tiene relación con el efecto de la validez de la clave en el PCCP.
6. El hecho de que la EDAN no estuviese afectada por la condición del ensayo previo indicaría que el efecto de validez/invalidez entre ensayos no es consecuencia de un sesgo atencional temprano, es decir, que la atención a la clave (representada por la EDAN) se mantiene independientemente de la condición del ensayo previo, por lo que la mayor o menor preparación para responder al target (representada por la amplitud de los componentes CNV y LRP) sería generada únicamente por la credibilidad asignada a la clave en cada ensayo.
7. El efecto de validez/invalidez entre ensayos generó una CNV más negativa, así como una LRP más positiva, en los ensayos precedidos por ensayos válidos, en comparación con los ensayos precedidos por ensayos inválidos. Ambas modulaciones se interpretarían como un incremento de la expectación/preparación (sensorial y motora), para percibir el target y emitir una respuesta, generada por la clave tras un ensayo válido.
8. La influencia de la condición del ensayo previo en la amplitud tanto de la CNV, como de la LRP, indicaría una actualización ensayo a ensayo de la credibilidad de la clave, lo cual se refleja en el patrón obtenido en los RTs (VV<IV<II<VI).

Arjona, A., Gómez, J., Gómez, C.M., 2017. Event related potentials changes associated with the processing of auditory valid and invalid targets as a function of previous trial validity in a Posner's paradigm. Neurosci Res, 115, 37-43.

1. El aumento de N1 en los ensayos válidos precedidos por un ensayo inválido (IV), en comparación con los ensayos válidos precedidos por otro ensayo válido (VV), posiblemente sea consecuencia de la menor predictibilidad y/o el mayor esfuerzo atencional requerido en un ensayo válido precedido por uno inválido.
2. Los componentes N1 y P2 estarían igualmente afectados por la PN, que se superpone y aumenta la amplitud del N1, pero disminuye la del P2, en los ensayos válidos precedidos por ensayos inválidos (IV), en comparación con los ensayos válidos precedidos por ensayos válidos (VV).
3. El incremento de la PN en los ensayos válidos precedidos por un ensayo inválido vendría originado por la menor preparación atencional y motora (CNV y LRP) que tiene lugar tras un ensayo inválido. La falta de credibilidad de la clave tras un ensayo inválido, daría lugar a un mayor esfuerzo atencional (representado por la PN) para procesar el siguiente target válido.
4. El hecho de que los componentes P3a y P3b presenten una mayor positividad en los ensayos inválidos precedidos por un ensayo válido (VI), en comparación con los ensayos inválidos precedidos por un ensayo inválido (II), indicaría que el estímulo target inválido es más inesperado tras un ensayo válido, lo que podría interpretarse como el origen de un mayor proceso de reorientación atencional (P3a), así como de una mayor actualización de la memoria de trabajo (P3b)
5. El cambio de validez de la clave (en este caso de válida a inválida) provoca que la invalidez sea más inesperada, y requiera un mayor análisis de error y una mayor

actualización de la credibilidad de la relación clave-target.

Arjona, A., Gómez, C.M., 2016. Cue validity probability influences neural processing of targets. Biol. Psychol. 119, 171–183.

1. Los resultados conductuales mostraron que a medida que aumenta la proporción de ensayos válidos por bloque (50%-68%-86%), la diferencia entre los RTs de los ensayos válidos e inválidos se hace más grande. Igualmente, la diferencia entre el porcentaje de respuestas incorrectas en los ensayos válidos e inválidos también creció a medida que aumentaba la proporción de ensayos válidos por bloque. Ambos efectos serían consecuencia del aumento de la proporción de ensayos válidos por bloque, ya que, con ello, aumenta la credibilidad de la clave, así como la preparación para responder correctamente en los ensayos válidos y erróneamente en los ensayos inválidos.
2. La ausencia de efectos significativos con respecto a la modulación de la CNV generada por el cambio en el porcentaje de validez del bloque, puede ser debida la escasa duración del periodo entre la clave y el target (360 ms), que impide la generación de una onda lenta más pronunciada (reflejando una mayor expectación por la llegada del target).
3. El aumento de amplitud de la CNV lateralizada en el bloque de 86%, en comparación con el bloque de 50%, indicaría que se produce una mayor preparación (no sólo motora, sino también sensorial) para emitir una respuesta en el lado indicado por la clave, cuando la proporción de ensayos válidos en el bloque es mayor. Cabe la posibilidad de que este incremento de la CNV lateralizada en el bloque de 86% represente también un incremento de la actividad basal del cerebro (Summerfield y de Lange, 2014).
4. El efecto del tipo de bloque sobre la amplitud del componente N1 auditivo pos-target posiblemente se vea compensado por las tendencias opuestas generadas por los efectos

atencionales (incremento de N1 en los ensayos válidos) y predictores (reducción de N1 en los ensayos válidos).

5. En el caso del componente P2a, la mayor diferencia entre condiciones (válida e inválida) en los bloques de 86% y 68%, en comparación con el bloque de 50%, posiblemente sea consecuencia de una mayor modulación atencional en los ensayos válidos, cuando estos son más probables.
6. La modalidad auditiva del componente P2p (reportado en Arjona y col., 2014a) mostró una mayor positividad en los ensayos inválidos, en comparación con los ensayos válidos, la cual (en base a la estructura jerárquica planteada por el modelo del cerebro Bayesiano (Friston, 2009), que plantea que las cortezas de orden inferior reciben información de las cortezas de orden superior para actualizar las probabilidades a priori), indicaría el proceso de actualización generado por cortezas de orden inferior en base al error de predicción.
7. La mayor positividad del componente P3a en los ensayos inválidos de los 3 tipos de bloques (50%, 68% y 86%) reflejaría una fuerte tendencia a la reorientación atencional ante la sorpresa, independientemente de la probabilidad a priori asignada la clave. En este sentido, la sorpresa podría considerarse como un proceso de todo o nada, más que una cantidad escalar modulable en intensidad.
8. La mayor amplitud del componente P3b en los ensayos inválidos, en comparación con los válidos, a medida que aumenta el porcentaje de ensayos válidos por bloque, indicaría que en los ensayos inválidos se produce una actualización del valor de la clave como predictora del target, y que esta actualización tiene más intensidad en función de que el porcentaje de ensayos inválidos sea menor (ya que el estímulo objetivo inválido se hace más inesperado al ser menos frecuente).
9. En conjunto, los resultados conductuales y neurales corroboraron los efectos de validez/invalidez de la clave y, además, muestran que existe una interacción (significativa

en algunos casos) entre el porcentaje de validez del bloque (50%, 68% y 86%) y la condición del ensayo (válido/inválido).

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ARTÍCULOS DEL COMPENDIO:

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PLoS one

Trial-by-Trial Changes in *a Priori* Informational Value of External Cues and Subjective Expectancies in Human Auditory Attention

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Abstract

Background: Preparatory activity based on *a priori* probabilities generated in previous trials and subjective expectancies would produce an attentional bias. However, preparation can be correct (valid) or incorrect (invalid) depending on the actual target stimulus. The alternation effect refers to the subjective expectancy that a target will not be repeated in the same position, causing RTs to increase if the target location is repeated. The present experiment, using the Posner's central cue paradigm, tries to demonstrate that not only the credibility of the cue, but also the expectancy about the next position of the target are changedin a trial by trial basis. Sequences of trials were analyzed.

Results: The results indicated an increase in RT benefits when sequences of two and three valid trials occurred. The analysis of errors indicated an increase in anticipatory behavior which grows as the number of valid trials is increased. On the other hand, there was also an RT benefit when a trial was preceded by trials in which the position of the target changed with respect to the current trial (alternation effect). Sequences of two alternations or two repetitions were faster than sequences of trials in which a pattern of repetition or alternation is broken.

Conclusions: Taken together, these results suggest that in Posner's central cue paradigm, and with regard to the anticipatory activity, the credibility of the external cue and of the endogenously anticipated patterns of target location are constantly updated. The results suggest that Bayesian rules are operating in the generation of anticipatory activity as a function of the previous trial's outcome, but also on biases or prior beliefs like the ''gambler fallacy''.

Citation: Arjona A, Gómez CM (2011) Trial-by-Trial Changes in *a Priori* Informational Value of External Cues and Subjective Expectancies in Human Auditory Attention. PLoS ONE 6(6): e21033. doi:10.1371/journal.pone.0021033

Editor: Jan Lauwereyns, Kyushu University, Japan

Received February 23, 2011; **Accepted** May 16, 2011; **Published** June 16, 2011

Funding: This work was supported by the Spanish Ministry of Science and Innovation, grant number PSI2010-17523 (http://www.micinn.es/portal/site/MICINN/menuitem.00d7c011ca2a3753222b7d1001432ea0/?vgnextoid=33881f4368aef110VgnVCM1000001034e20aRCRD), and Junta de Andaluci, grant number CTS-153 (http://www.juntadeandalucia.es/servicios/ayudas/novedades.html). No additional external funding received for this study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

The attentional function allows the selection of relevant stimuli and appropriate responses. This selection is related to the evaluation of cues and contexts in which the stimuli are inserted. Biasing the neural activity of some percepts would make it possible to produce faster responses if these stimuli appear. Attentional control is particularly important in situations where there are new and complex tasks where the nature of the stimuli and/or responses is uncertain. Preparatory activity based on *a priori* probabilities generated in previous encounters with similar situations would produce a bias for the selection of stimuli and actions adapted to the current context [1]. The counterpart of the preparation process is that it can be correct (valid) or incorrect (invalid); depending on the actual stimulus that appears after preparation, a reduction or an increase in RTs would be expected, respectively.

Posner's central cue paradigm (PCCP) is particularly appropriate for testing congruency between the expected and current stimuli. In this paradigm, the central cue may validly (V trials) or invalidly (I trials) indicate the spatial position of the upcoming target. If the cue is a valid predictor of the target, there is a benefit in the RT with respect to neutral cues. However, if the target is incorrectly cued, a cost occurs in the RT with respect to neutral cues [2], [3]. This effect is termed as a cost-benefit or validity-invalidity effect [2]. This effect would be due not only to the preparation of the sensory cortices related to the predicted spatial location of the target [4,5,6], but also partly to preparation for the correct response forvalidly cued target stimuli [7], [5]. Invalidly cued targets would increase their RTs because of the need to reorient the attention and set up the contralateral network to the one preactivated during the preparation period.

An important issue that has scarcely been studied in PCCP is how a correct or incorrect prediction in a given trial can induce changes in the processing of the next trial, i.e. sequential effects. A recent behavioral report on the PCCP addresses this point [8]. These authors found an interaction between the validity in preceding trial and the validity in current trial: the benefits in RTs when compared to neutral cues are greater if a valid trial is preceded by a valid trial (VV trials) rather than an invalid one (IV);

but also these authors also found the cost of an invalid trial is greater if it is preceded by a valid trial (VI trials) than by an invalid one (II trials). These results have recently been replicated [9]. We would use the terminology of sequential validity effect to term the interaction between the validity of current and preceding trial. A detailed error analysis has not yet been computed in the sequential validity effect. Other effects related to neutral and catch trials, to the effects of alternate or repeated responses, and to the inhibition of return are also reported by Jongen and Smulders (2007).

These results have recently been interpreted [10] in the sense that PCCP could be considered a very simple form of a cognitive cycle. In this cycle, the preparation, evaluation of the trial, and transfer of information to the next trial would occur sequentially. During the preparation period, the cue would bias the neural set related to the active cue in the direction indicated by the cue, and an *a priori* probability would be assigned to the cue, determining the amount of attentional resources that would be deployed to the indicated location. The Contingent Negative Variation would be the electrophysiological marker of this preparatory period [5],[6]. During the evaluation period, the valid or invalid nature of the trial would be assessed, with the P3a and P3b being the psychophysiological markers of this cognitive operation [11,7,12]. Finally, transfer of information to the next trial would allow a continuous change in the *a priori* credibility that subjects assign to the cues [10]. The credibility would be operationalized as the conditioned probability that, given the cue (S1 stimulus), a target stimulus (S2) would appear in the indicated location (p (S1/S2)). This *a priori* information would be constantly updated, and the P3b component would index the change in this probabilistic value associated with the cue [13], [14]. The key point in the analysis of sequences is that some information can be carried over from one trial to the next. The Bayesian brain perspective fits well with the notion of changing the *a priori* probabilities of the S1–S2 relationship, because it involves the updating of beliefs about subsequent targets based on cues in current and previous trials [15], [16]. In computational terms these ideas are embedded in the Bayesian computational framework proposed by Friston[15], [17], in which neural networks would establish predictions about the credibility they assign to certain environmental cues, and as consequence of the trial outcome the neural networks implicated in this task would change the synaptic weights in order to make better predictions of the cue predictive value in the next future. The changes in early P1 and N1 to attended targets would reflect the confirmation of predicted target (increased precision), while the increase of P3 to invalid targets would reflect the change in the internal model about the precision of the target prediction.

Another issue related to the analysis of sequences is the first-order sequential effect, i.e. the dependency of the response in the current trial on the response in the previous trial. Among the most conspicuous effects are the first-order effects due to the preceding stimulus, whether they are equal to (repetition) or different from (alternation) the preceding stimulus [18]. These first-order effects are dependent on the time elapsed from the current stimulus to the preceding response: the so-called response stimulus interval (RSI). The most common effect is that, for short RSI (less than 500 ms), the reaction time is shorter for repeated stimuli than for alternate stimuli. When the RSI exceeds 500 ms, the repetition effect decreases, and in some cases can become an alternating effect [19]. This differential effect for short and long RSI has been attributed to two different mechanisms [20], [18]. The repetition effect during short RSI could be due to an automatic facilitation. The alternation effect during long RSI can be explained by biasing the probability of which stimulus will be next. The process is controlled by an increased expectancy of the stimulus opposite to the one previously presented. This process is similar to the so called "gambler's fallacy", where subjects believe that conditioned probability exists between an event and the previous one, when in reality the two events are completely independent. At first glance, the Gamblers fallacy may appear to be a false belief. However, in a changing world, this fallacy may actually be a truthful prior belief that (on average) optimises responses. In short, we may have the prior expectation that things alternate, these sorts of priors have been discussed as an explanation for perceptual switches in bistable perception. Here, we conjecture that subjects believe a priori that targets will appear in alternating locations, at least for two trials sequences (see below).

The study of Event Related Potentials (ERPs) tends to support the view that subjects prepare the response opposite to the one previously executed [21]. In that particular experiment, a tone with a different frequency signaled the response hand. The lateralized readiness response (LRP component) showed that subjects prepared responses corresponding to the hand that had not been used in the previous stimulus [21]; that is, they prepared the alternate response. If the arriving stimulus is the same as the one previously presented, a correction of the movement occurs that is reflected as a change of trend in the LRP component. Similar LRP behavior has been obtained when visual stimuli, rather than auditory tones, are used [5].

However, the sequences of alternation or repetitions would also be able to affect the RTs of subjects as higher order repetition-alternation effects. The most common pattern is of shorter RTs if the higher order pattern is continued, series of repetitions or alternations, than if the pattern is discontinued, i.e. an alternation preceded by series of repetitions [22], [23]. This pattern of RTs could also be included in the framework of the gambler's fallacy if a more broad interpretation of the prior belief is taken, in which it can be assumed that the subjects are looking for certain patterns, series of repetitions or alternations. However it must be remarked that this higher order sequences effects are occurring simultaneously with first-order sequential effects which are the more prevalent effects.

The main aim of the present study was to analyze the sequential effects of S1–S2 trials preceded by other S1–S2s, taking into account the validity/invalidity character of the current and preceding trials. We expect the outcome of the current trial to affect the behavior on the next one. More specifically, in the present report we will try to analyze the sequential dependency of RTs as a function of the validity history of previous trials. Sequences of two and three trials would be analyzed. The hypothesis would be that the validity effect would increase with trial sequence validity because of an increased focused attention on the cued location. In contrast, the invalidity effect would decrease with trialsequence invalidity if less attention is deployed to the cued location. These results would suggest that the deployment of attention would be a function of the validity assigned to the predictive cue as a function of the validity/invalidity history. Not only RTs but also errors should fit this description. Sequences of valid trials should produce not only a decreased reaction time but also an increase in anticipatory responses due to over-preparation. The anticipatory responses would also be expressed as incorrect responses in the invalid trials. An important point about the present experiment is that the cue was visual but the target was an auditory monoaural stimulus, eliminating the possibility that residual eye movements would have any influence on response times or error production.

Additionally, the possibility that a first-order sequential effect would also bias the preparation for the incoming imperative stimuli was tested. For this objective the RTs to the auditory

targets when the previous trial differed (Alternation: A), or not (Repetition: R), with respect to the stimulated ear would be compared. The analysis of sequences of Alternation-Alternation (A-A) vs. Repetition-Alternation (R-A) and Repetition-Repetition (R-R) vs. Alternation-Repetition (A-R) were also analyzed in RTs and type of errors. Thesesequenceswere selected to explore the effects on behavior of the confirmation or disconfirmation of repetition and alternation patterns. Furthermore, second-order sequential effect for trials ending in alternation or repetition would be tested to evaluate how prior information about target location can be challenged by experience. The specific hypothesis were: (i) A repeated trial preceded by a repeated trial should have shorter RTs than preceded by an alternation trial (R-R<A-R); and (ii) an alternation trial preceded by an alternation trial should have shorter RTs than preceded by a repeated trial (A-A<R-A).

Methods

Participants

Thirty-four subjects (17 female and 17 male, 30 right-handed and 4 left-handed) between 19 and 35 years of age (mean 27) took part in the experiment. The experiments were conducted with the informed and written consent of each subject, following the rules of the Helsinki Convention. The Ethics Committee of the University of Seville approved the study.

Stimuli and behavioral paradigm

The stimulus presentation and response recording were computer-controlled (E-Prime 2.0). Participants were seated 60 cm from a computer screen. The subjects participated in a modified version of the PCCP in which the central cues were arrows appearing in the center of the screen, followed by monoaural auditory stimulation. The auditory stimuli were delivered to the subject's ears through headphones. Participants were asked to fix their eyes on a white cross in the center of the screen, and they were instructed to pay attention to the ear signaled by the central arrow, and then press the right button as quickly as possible if the auditory stimulus appeared in the right ear, or the left button if the auditory stimulus appeared in the left ear. The response device was the Cedrus model RB-530. The arrow stimulus was considered the spatial orientation cue, and the monoaural auditory stimulus was the imperative one. The event sequence within a trial was as follows: the central arrow pointer was on for 300 ms (Figure 1), followed by an expectancy period in which a central fixation white cross appeared for 300 ms. Therefore, the total S1–S2 period was 600 ms. The auditory stimulus (1000 Hz) lasted for 100 ms and was randomly presented to the left and right ear with equal probability (0.5). The time of response was 1000 ms., followed by a 300 ms period (Figure 1), producing a total inter-trial interval of 1300 ms.

Each subject was presented with a total of 500 trials divided into five blocks. The central warning stimulus had directional information: in half of the trials it pointed to the right, and in the other half to the left. In 80% of the trials the arrow gave valid information about the target ear (V: valid trials), and in 20% of the trials, the arrow pointed to the ear opposite to where the auditory stimulus would appear (I: invalid trials). The cued location (left or right ear) and the trial Validity or Invalidity were selected randomly. Thus, the experiment presented four types of trials: left valid (LV: 200 trials), right valid (RV: 200 trials), left invalid (LI: 50 trials), and right invalid (RI: 50 trials). It should be noted that left/right in the experimental condition refers to the localization of the auditory stimulus and not the directionality of the warning/arrow stimulus. Therefore, the LI condition refers to preparation of the right side, although the actual target appears in the left ear. The situation is the same for the RI: a left target is indicated by the central cue, but a right target appears. The subjects had to respond to the monaural auditory stimulus with the index finger of the compatible hand. They were informed that the visual cue had an informative value, indicating with high probability the location of the auditory stimulus. RTs and proportion of correct and incorrect responses (responses to the side opposite the stimulated ear), anticipations (responses of targets faster than 180 ms after the auditory target), and omission responses were computed. The percentage of total errors was computed as the sum of all types of errors.

Behavioral statistical analysis

In the present report, we will focus on the behavioral effects of valid and invalid trials preceded by validly or invalidly cued trials. Therefore we will consider four different types of sequencesof two trials(dyads): valid trials preceded by a valid one (VV) (mean of trials: 316.2 trials, 63.87% of the total, range between different subjects: 310–328); valid trials preceded by an invalid one (IV) (79.7 trials, 16.10% of the total, range: 70–86); invalid trials preceded by a valid one (VI) (79.5 trials, 16.06% of the total, range: 68–87); and invalid trials preceded by an invalid one (II) (19.4 trials, 3.91% of the total, range: 12–29). The different number of trials for different subjects is due to the random selection of trials in each block. In addition, the RTs and errors from sequences of three trials (triads) were computed. The triads were: VVV (250 trials, 51.02% of the total, range: 236–271), IVV (62.8 trials, 12.81% of the total, range: 54–70), VIV (63.2 trials, 12.89% of the total, range: 49–73), IIV (15.7 trials, 3.21% of the total, range: 11–20) III (3.5 trials, 0.71% of the total, range: 0–10), VII (15.7 trials, 3.21% of the total, range: 11–20), IVI (15.9 trials, 3.24% of the total, range: 11–26), VVI (62.9 trials, 12.83% of the total, range: 55–71).

For the dyads of trials, repeated measures ANOVAs for RTs (only for correct responses) and the different types of errors were computed. Three factors were considered: type of sequence (VV, IV, II and VI), side of target presentation (left and right), and whether in the current trial there was alternation or repetition in the position of the target with respect to the previous trial (A vs. R). In the ANOVAs, if a subject presented zero correct responses for any condition, s/he was excluded from the analysis. Our post hoc comparisons were adjusted for multiple comparisons using the Bonferroni correction. We will refer to these as Bonferroni comparisons. The reported p values are already corrected by multiple comparisons.

Repeated measures one-way ANOVA was computed for the statistical analysis of triads. In this case, the triads ending with valid and invalid trials were analyzed separately. Given that our hypothesis was that the deployment of attention would be a function of the trial sequence, only planned *a priori* comparisons-were computed. The comparisons for triads ending with a valid trial were VVV vs. IVV and IVV vs. IIV. The comparisons for triads ending with an invalid trial were III vs. VII and VII vs. VVI. These comparisons were computed for both RTs and Errors.

We also examined alternations of target location in triads. Sequences of Alternation-Alternation (A-A) vs. Repetition-Alternation (R-A), and Repetition-Repetition (R-R) vs. Alternation-Repetition (A-R) were also analyzed in RTs and type of errors by means of a paired t-test.

Results

The ANOVA of RTs of sequences of two trials showed a statistically significant effect of the Alternation-Repetitionfactor ($F\ [1,31] = 5.319,\ p < 0.028$ (mean of Alternation = 357.8166,

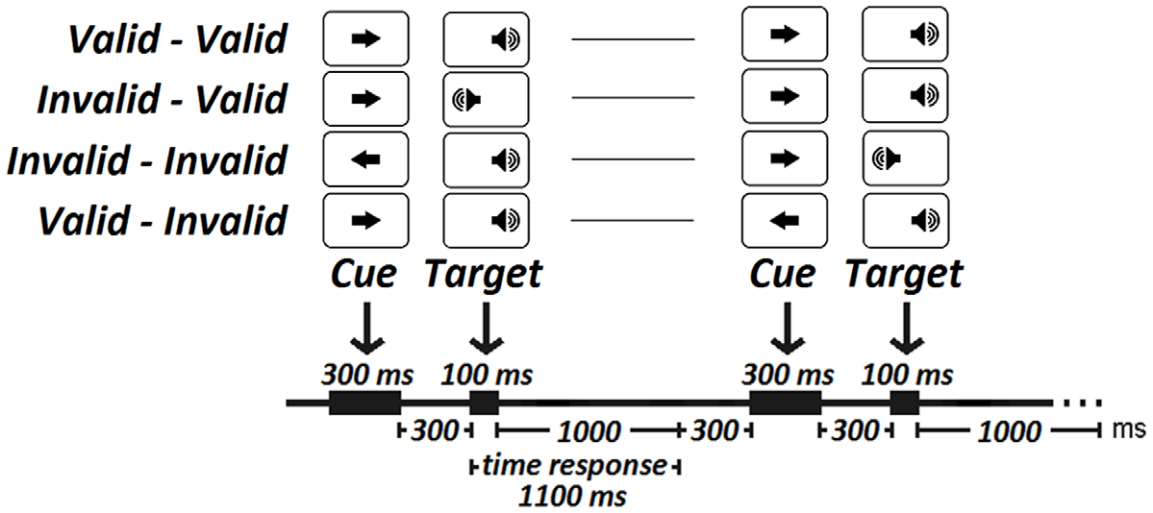

Figure 1. Paradigm for the experiment. The different types of sequence trials (dyads) considered in the experiment are shown. The temporal sequence of stimulus presentation appears in the lower part of the figure. The central arrow was presented in the center of the screen, and the auditory target was presented monoaurally. Notice that the RTs were obtained from the S2 stimulus in the second trial. This corresponds to the stimulus on the right side of the figure in each stimulus sequence.
doi:10.1371/journal.pone.0021033.g001

SD = ±73.32405; mean of Repetition = 365.4573, SD = ±75.38 355). The factor type of sequence was also statistically significant ($F\ [2.155,\ 66.804] = 48.789$, $p<0.001$(Figure 2A). No interaction of the effects was obtained. Only 32 subjects were entered in this ANOVA because two of them did not present any correct response for the II condition.

Analysis of type of sequences

The Bonferroni comparisons contrast showed statistically significant differences between sequences VV-IV ($p<0.006$), VV vs. II ($p<0.006$), VV-VI ($p<0.006$), IV-II ($p<0.006$) and IV-VI ($p<0.006$). The comparison of the II-VI conditions was only significant if the Bonferroni correction was not applied ($p<0.046$), probably because of the low number of trials in the II condition (19.4 trials, 3.91% of the total). The pattern of RTs in the two trials sequences can be seen in Figure 2A.

An error analysis of the two trial sequences was performed. The one-way ANOVA in the different sequences was statistically significant for the total errors ($F\ [1.517,\ 47.025] = 7.494$, $p<0.003$); the anticipations errors ($F\ [1.118,\ 34.670] = 7$, $p<0.010$); and the incorrect responses ($F\ [2.065,\ 64.004] = 17.560$, $p<0.001$). Table 1 shows the mean percentages and standard deviations for the different types of errors. (N = 32). Figure 2B shows the inverse pattern for the percentage of anticipatory and incorrect response errors.

The Bonferroni comparisons contrast showed statistically significant differences for incorrect responses between VV-VI ($p<0.006$), IV-VI ($p<0.006$) and II-VI ($p<0.006$); for anticipations between VV-IV ($p<0.018$) and VV-VI ($p<0.042$); and for total errors between VV-IV ($p<0.030$), VV-II ($p<0.030$), IV-VI ($p<0.054$) and II-VI ($p<0.006$). Figure 3A shows the relationship of the correct response RTs with the percentage of anticipations. This was an inverse relationship, indicating that faster subjects also produced the largest number of anticipations.

An additional comparison was made between the RTs of the incorrect responses in the VI condition and those of the correct

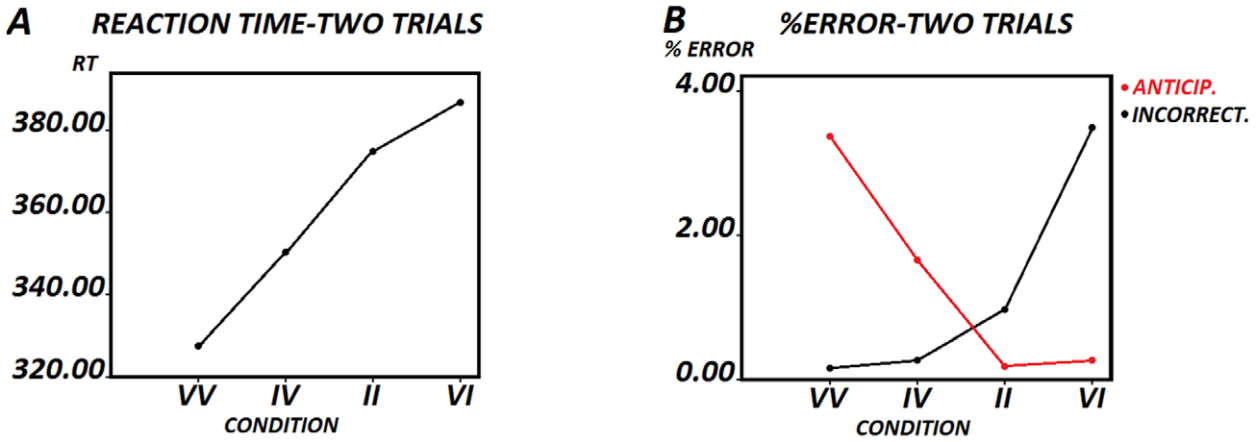

Figure 2. Behavior in the two trial sequences. Fig. 2 Ashows the reaction times in the Valid-Valid (VV), Invalid-Valid (IV), Invalid-Invalid (II) and Valid-Invalid (VI) conditions. Fig. 2B showsthe percentage of anticipatory and incorrect responses in the different sequences. Notice the low percentage of errors and the inverse pattern between anticipatory and incorrect responses.
doi:10.1371/journal.pone.0021033.g002

Table 1. Percentage of errors: sequences of two trials.

Condition	VV		IV		II		VI	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Incorrect	0.16%	0.32	0.27%	0.68	0.97%	3.20	3.49%	2.97
Anticipation	3.38%	6.62	1.65%	4.16	0.18%	1.03	0.27%	0.61
Omission	0.56%	0.83	0.35%	0.80	0.14%	0.84	0.59%	1.54
Total	4.09%	7.28	2.30%	4.55	1.31%	3.38	4.36%	3.75

doi:10.1371/journal.pone.0021033.t001

responses in the same condition. This comparison was made to check whether the incorrect responses were due to very fast responses in which not enough auditory information was gathered. The repeated measures t-test showed a statistically significant difference in correct vs. incorrect responses in the VI condition ($F\ [1,27] = 21.730$, $p<0.001$; mean of RTs incorrect responses = 387.1751, SD = ±89.6058; mean of RTs in incorrect responses = 319.3455, SD = ±113.1817) (N = 28). Given the low number of incorrect responses, six subjects did not show any incorrect response and were not included in the analysis. Figure 3B shows the relationship between the RTs of correct responses and the percentage of incorrect responses. Figure 3C shows the relationship between the RTs of incorrect responses and the percentage of incorrect responses. If graphs 3B and 3C are compared, the faster RTs of incorrect responses with respect to RTs of correct responses can be observed. Another additional point of VI trials is that the percentage of incorrect responses did not show an inverse relationship with RTs (as in figure 3A), suggesting that these errors are not exclusively due to anticipatory behavior.

The ANOVA of the reaction times of sequences with three trials ending in a valid trial (VVV, IVV, VIV, IIV) showed a statistically significant effect for the *type of sequence* factor ($F\ [1.759, 58.052] = 22.772$, $p<0.001$ (Figure 4A)(N = 34). The reason there are 34 subjects in the triad analysis, while in the dyads there are only 32, is that in triads the left and right target conditions were collapsed. The planned Bonferroni comparisons contrast showed statistically significant differences between sequences VVV-IVV ($p<0.002$) and IVV-IIV ($p<0.002$). (N = 34). Figure 3D shows the relationship between the correct response RTs and the percentage of anticipations. This was an inverse relationship, indicating that faster subjects are also those producing a greater number of anticipations. The errors from the trial sequences ending with a valid trial were analyzed. The one-way ANOVA was statistically significant only for the total errors in the different sequences ($F\ [1.350, 44.555] = 4.459$, $P<0.030$). Table 2 and Figure 4B shows the mean percentages and standard deviations. (N = 34). The planned Bonferroni comparisons showed statistically significant differences for total errors between VVV-IVV ($p<0.016$), but not between IVV-IIV ($p<0.404$).

The ANOVA of the reaction times for sequences with three trials ending with an invalid trial (III, VII, IVI, VVI) did not show a statistically significant effect for the factor *type of sequence* ($F\ [1.506,$

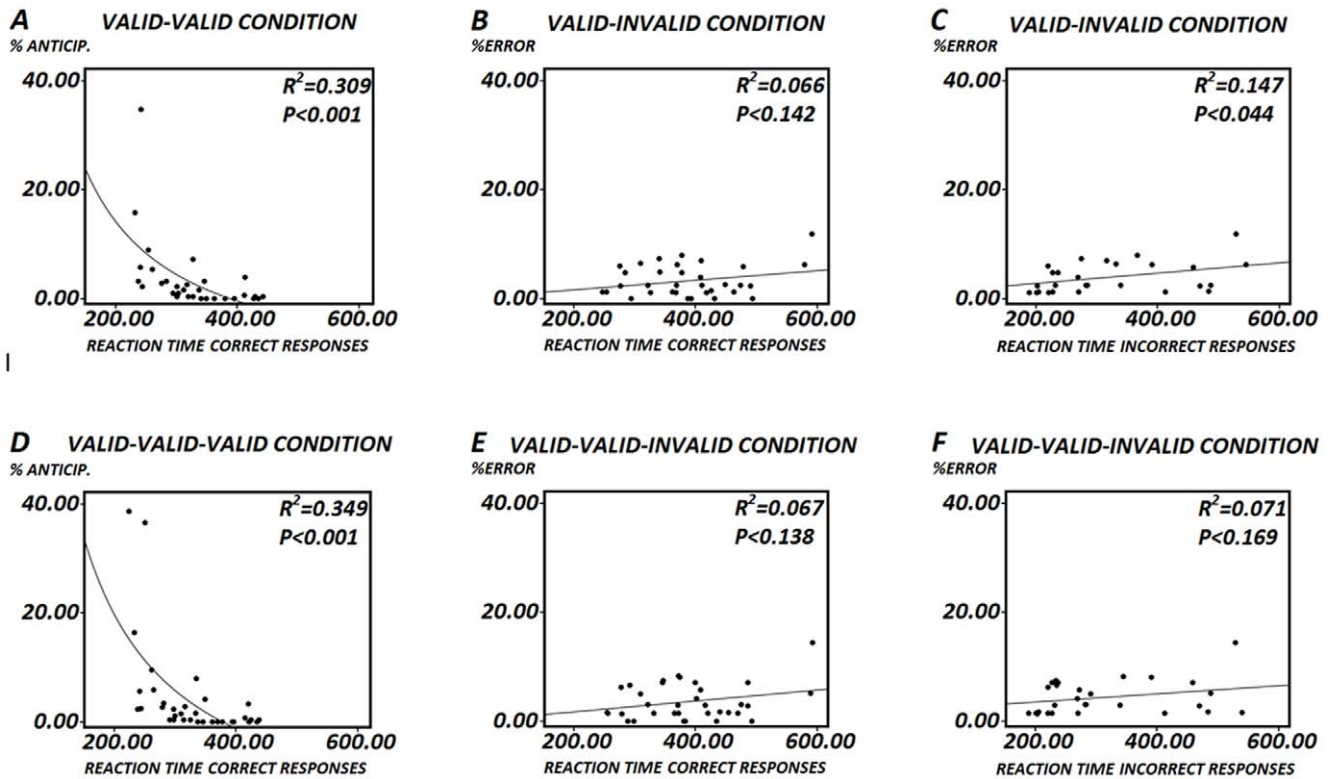

Figure 3. Relationship between errors and reaction times. Fig. 3A shows the relationship of the correct response RTs with the percentage of anticipation errors in the valid-valid condition. This relationship was modeled as an inverse equation by means of a polynomial fit. Fig. 3B shows the relationship between the RTs of correct responses and the percentage of incorrect responses in the invalid-valid condition. Fig. 3C shows the relationship between the RTs of incorrect responses and the percentage of incorrect responses. If graphs 3B and 3C are compared, faster RTs of incorrect responses with respect to RTs of correct responses can be observed. Figs. 3D, 3E and 3F show the same information as 3A, 3B and 3C, but for the valid-valid-invalid sequence. Also notice that only the data in Figs. 3A and 3D can be fitted by an inverse relationship.
doi:10.1371/journal.pone.0021033.g003

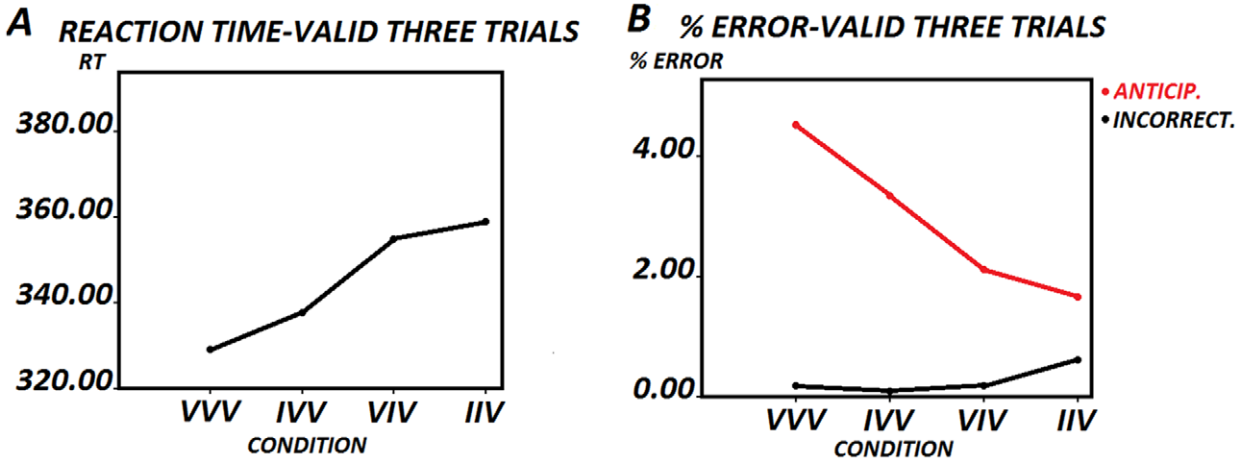

Figure 4. Behavior in the three trial sequences (triads) ending in a valid trial. Fig. 4A shows the reaction times in the Valid-Valid-Valid (VVV), Invalid-Valid-Valid (IVV), Valid-Invalid-Valid (VIV) and Invalid-Invalid-Valid (IIV) conditions. Fig. 2B shows the percentage of anticipatory and incorrect responses in the different sequences. Notice the low percentage of errors and the inverse pattern between anticipatory and incorrect responses.
doi:10.1371/journal.pone.0021033.g004

45.166] = 1.600, p<0.216 (Fig. 5A). (N = 31; because there were 3 subjects who did not present any case in the III condition). The errors from three trial sequences ending with an invalid trial were also analyzed. The one-way ANOVA was statistically significant only for the total errors in the different sequences (*F [1.911, 63.076] = 3.785, p<0.030*). Table 3 and Figure 5B show the mean percentages and standard deviations. (N = 34). Finally, the planned Bonferroni comparisons showed a statistically significant difference for total error between VII-VVI *(p<0.002)*, but not between III-VII *(p<1.626)*.

An additional comparison was made between the RTs of the incorrect responses in the VVI condition and those of the correct responses in the same condition. The repeated measures t-test showed a statistically significant difference in correct vs. incorrect responses in the VVI condition (*F [1,27], p<0.001*; mean of RTS of correct responses = 392.0075, SD = ±90.2392; mean of RTs of incorrect responses = 313.8533, SD = ±113.6903). Given the low number of incorrect responses, six subjects did not show any incorrect response and were not included in the analysis. Figure 3E shows the relationship between the RTs of correct responses and the percentage of incorrect responses. Figure 3F shows the relationship between the RTs of incorrect responses and the percentage of incorrect responses. If graphs 3B and 3C, and 3D and 3F, are compared, it can be seen that the RTs of incorrect responses are faster than the RTs of correct responses.

Table 2. Percentage of errors: sequences of three trials ending in a valid trial.

Condition	VVV		IVV		VIV		IIV	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Incorrect	0.18%	0.34	0.09%	0.38	0.19%	0.67	0.61%	2.05
Anticipation	4.50%	9.16	3.33%	6.67	2.11%	5.14	1.64%	3.57
Omission	0.63%	0.96	0.24%	0.72	0.36%	0.94	0.16%	0.95
Total	5.32%	9.91	3.67%	7.21	2.67%	5.36	2.42%	4.11

doi:10.1371/journal.pone.0021033.t002

Analysis of thefirst-order and second-ordersequential effects of the Alternation and Repetition factor

The errors for the Alternation and Repetition factorwere analyzed. The one-way ANOVA was statistically significant only for the incorrect responses (*F [1,31] = 10.847, p<0.002*). Table 4 shows the mean percentages and standard deviations. (N = 32).

As previous results indicated faster RTs in the Alternation condition than in the Repetition condition, the possibility that a confirmatory hypothesis would also be acting to modulate the RT was checked by means of a comparison of the A-A vs. R-Aand R-R vs. A-R sequences. If subjects presented a false belief of the gambler's fallacy type, A-A sequences would imply a confirmation of this belief, and RTs should be faster than in the R-A sequences, where this belief was disconfirmed in the previous trial. Results for RTs are presented in Figure 6 and errors are presented in Table 5. The same argument stands for second order sequential effects in which the last trial is a repetition. The paired t-test showed that there was a decreased RTs in the R-R condition with respect to the A-R condition, (*p<0.001*) (Figure 6). Furthermore, there was a statistically significant higher number of incorrect responses in the condition A-R than in the R-R condition(*p<0.007*).

Discussion

The results indicate an increase in RT benefits when dyads and triads of valid trials occurred. The analysis of errors indicates an increase in anticipatory behavior that grows in VV sequences compared to IV and VI sequences. There was a statistical trend of increased costs in the dyads of II trials with respect to invalid trials preceded by valid trials (VI). The analysis of errors showed an increase in incorrect responses in sequences ending in invalid trials, while anticipatory responses were very low in the VI and II trials. On the other hand, there was also a benefit in RTs and a reduced number of incorrect responses when a trial was preceded by trials in which the position of the targets was different from that of the current trial(first-order alternation effect). Furthermore RTs of A-A trial sequences were faster than R-A sequences and R-R were faster than A-R. Taken together, these results suggest that in central PCCP, the anticipatory activity, the validity-invalidity effect, and the alternating effect are modulated by the previous trial sequences. This sequential modulation has two independent sources: (i) a previous-trial validity dependent preparatory activity

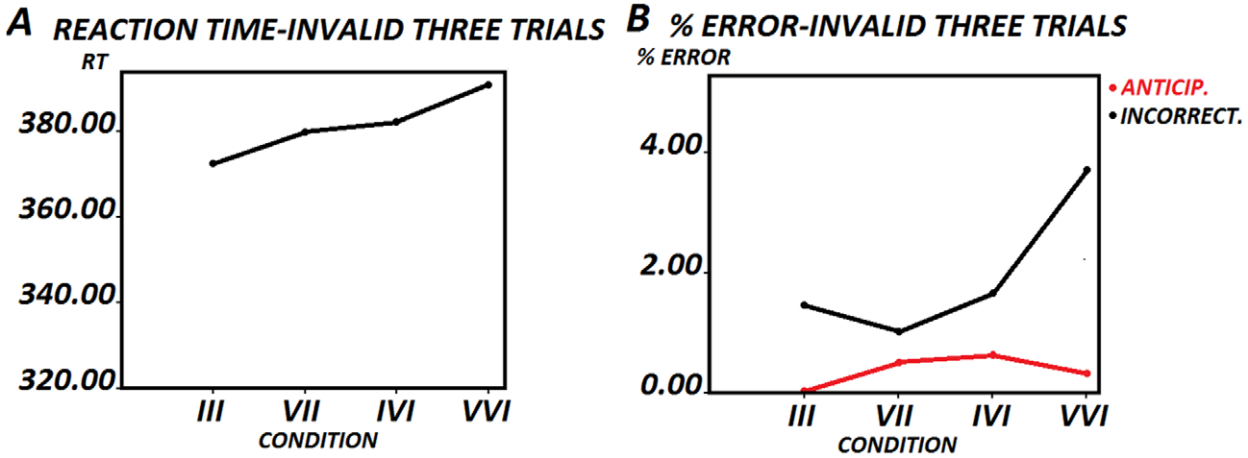

Figure 5. RTs in the three trial sequences (triads) ending in a valid trial. Fig. 5A shows the reaction times in the Invalid-Invalid-Invalid (III), Valid-Invalid-Invalid (VII), Invalid-Valid-Invalid (IVI) and Invalid-Invalid-Valid (IIV) conditions. Fig. 2B shows the percentage of anticipatory and incorrect responses in the different sequences.
doi:10.1371/journal.pone.0021033.g005

and (ii) a previous-target location dependent preparatory activity. The results suggest that Bayesian rules tend to operate in generating anticipatory activity based on confirmatory outcomes of explicit cues, but also based on confirmatory outcomes of priors, as in the ''gambler's fallacy.

Sequential validity effects

In the present experiment, the trials ending with valid conditions (VV and IV) were faster than the trials ending with invalidly cued targets (VI, II), fitting the classically described cost-benefit pattern of the PCCP [2]. The current theory on how valid cueing is able to decrease reaction times is based on data suggesting that directional cues activate the opposite sensory cortex to the signaled hemifield, facilitating perceptual activities once the sensory stimulus arrives [11,4–6]. Another source for facilitating responses to valid cues would be the anticipatory neural activity in motor and premotor cortices needed for the response to the expected target [5]. In this way, attention during the PCCP can be related to the idea of Bayesian inference, in the sense that the subject is making predictions about the possible position of the target, inducing a pre-activation of the areas supposedly needed for the next incoming target. This framework makes it possible to explain not only benefits, but also RT costs, given that the whole network must be reorganized when an invalidly cued target is presented. These ideas also fit the biased competition model [1], given that a central executive would make it possible to boost activity in selective sensory cortices related to the predicted perception, favoring its perception over any other competing stimulus. The dorsolateral fronto-parietal network would be the key attentional structures feeding the sensory cortices with neural inputs that would increase the gain in the predicted positions [24]. For invalidly cued targets, the right inferior frontal gyrus would be one of the key areas participating in denoting the novel character of the target [25], [24].

However, the main objective of the present report is related to the sequential validity effect [8], [9]. As indicated above, the targets in the last trials in sequences of VV and VVV trials correspond to the dyads' and triads' fastest RTs conditions, but they are also the conditions with the highest number of anticipations, indicating that, in part, the increased RTs correspond to hand movements without enough available information. However the low number of errors make difficult to assume that all the sequential validity effect is due to pure anticipatory responses, rather than to preparatory attention. The pattern of RTs follows the rule of VV<IV<II<VI. The pattern of II<VI is particularly important to support the idea of preparatory attention for the sequential validity effects [4–6]. This result suggest that if an invalid trial is preceded by an invalid trial the subjects deployed less attention to the indicated ear, and responses are faster than in VI trials, in which more credibility is assigned to the cue and responses are consequently delayed. The RTs patterns for triads suggest also a trial-by-trial change of the intensity of deployed attention. The patterns for the triads corresponds to a statistically significant pattern of VVV<IVV<IIV, and a

Table 3. Percentage of errors: sequences of three trials ending in a invalid trial.

Condition	III		VII		IVI		VVI	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Incorrect	1.47%	8.57	1.03%	3.15	1.66%	3.46	3.71%	3.38
Anticipation	0%	0	0.52%	2.19	0.65%	2.15	0.34%	0.90
Omission	0%	0	0.19%	1.14	0.44%	1.80	0.61%	1.90
Total	1.47%	8.57	1.75%	3.78	2.75%	4.67	4.67%	4.04

doi:10.1371/journal.pone.0021033.t003

Table 4. Percentage of errors: first order repetition-alternation effects.

Condition	A		R	
	Mean	SD	Mean	SD
Incorrect	0.53%	0.69	1.00%	0.75
Anticipation	1.86%	3.02	1.54%	3.02
Omission	0.29%	0.47	0.36%	0.43
Total	2.69%	3.47	2.91%	3.50

doi:10.1371/journal.pone.0021033.t004

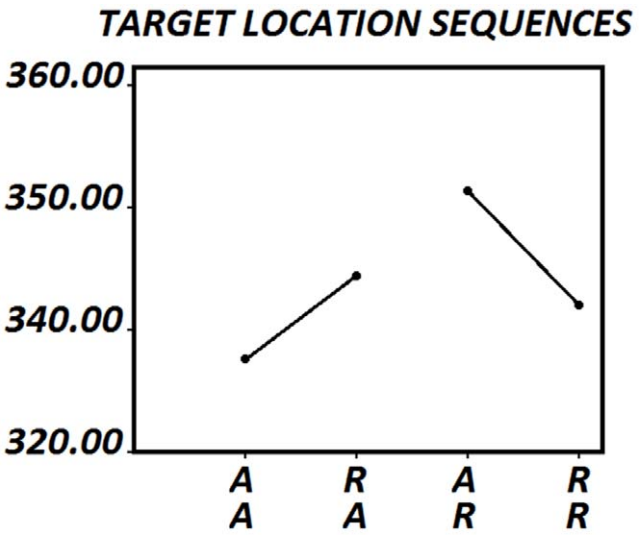

Figure 6. RTs to second-order alternation repetition effects. A-A: sequences of two alternations in target locations (i.e. left-right-left). R-A: Sequences of repetition and alternation of target location (i.e. left-left-right). A-R: Sequences of alternation and repetition of target location (i.e. left-right-right). R-R: Sequences of repetition and repetition of target location (i.e. left-left-left).
doi:10.1371/journal.pone.0021033.g006

qualitative pattern of III<VII<VVI (probably not statistically significant due to the low number of trials).

The pattern of errors is an increased number of anticipations in the VV sequences, and an increased number of incorrect responses in the VI conditions, while the anticipation remains very low in the VI condition. Moreover, incorrect responses are faster than correct responses in VI (and VVI) sequences. Interestingly, while the relationship between percentage of anticipations and RTs was an inverse relationship (Fig. 3A), the same relationship did not occur with incorrect responses (figs 3B and 3C). These results indicate that incorrect responses are too-fast responses in which not enough auditory information has been gathered, but they are not purely anticipatory as in the VV condition, indicating that a trial being preceded by a valid trial generates anticipatory activity that, in general, is not enough to trigger a movement, but that can increase the number of errors. Therefore, attentional bias in the sequences is observed as anticipatory in VV trials and as incorrect responses in VI trials. It is possible that there is a response latency time in which sensory information is gathered, thus influencing behavior, but the responses are so fast that a weighting average of the exogenous information with the endogenous information occurs. This interaction between endogenous (anticipatory) and exogenous (sensory) activity has been proposed for the express saccades [26]. The express saccades is an ideal paradigm for studying this "intertidal" period because in the superior colliculus there is vectorially weighted predictive and visual coding, producing saccades whose precision amplitude errors, measured in visual angle degrees, have an inverse relationship with latency time [26]. In the experiment reported here, the anticipatory behavior in VV condition would be a synergy between the prediction and the sensory information, while the incorrect responses in VI condition would reflect the incongruency between prediction and the actual stimulus. The present report contains enough quantitative description of the experimental results in order to produce a mathematical modeling of the RTs an errors pattern of these sequential analysis. Therefore, the suggestion of a response inter-tidal period in which information that a target is present producing anticipatory responses in VV trials and incorrect fast responses in VI trials remains to be modelized. This inter-tidal period would be similar to the intermediate phase (responses between 200–300 ms) of incompatible noise trials in the "noise-compatibility paradigm", in which the presence of incompatible letters activate the incorrect response producing more errors than for long latency responses (more than 300 ms) which would be more accurate [27].

Table 5. Percentage of errors: second order repetition-alternation effects.

Condition	A-A		R-A		R-R		A-R	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Incorrect	0.33%	0.65	0.49%	0.59	0.43%	0.84	1.08%	0.96
Anticipation	1.98%	3.38	1.53%	2.52	1.66%	2.59	1.09%	2
Omission	0.25%	0.46	0.25%	0.57	0.28%	0.47	0.31%	0.49
Total	2.57%	3.39	2.29%	2.60	2.39%	2.7	2.48%	2.37

doi:10.1371/journal.pone.0021033.t005

The patterns obtained for RTs and errors suggest that information is being transferred from one trial to another, so that a confirmation of the explicit hypothesis about the position of the next target encoded by the cue is transferred to the next trial and, consequently, influences the level of attention. This argument is related to the proposal by Yu and Dayan (2005) [28], when analyzing the cost-benefit pattern, in which they highlight the balancing of the relative influence of bottom-up sensory information and top-down prior expectations by weighting them according to their relative precision (credibility). Indeed, it has been proposed that attention can be understood purely in terms of optimizing the precision or credibility of representations during hierarchical inference in the brain [16]. Therefore, one possible explanation for the longer RTs in the IV condition than in the VV condition (and VI with respect to II) would be continuous updating of the predictive value subjects assign to the spatial cue. Yu and Dayan (2005) [28] proposed that PCCP is a good example of how probabilistic Bayesian learning occurs. In trials in which expectations are violated, the subjects would pay less attention to top–down signals (cues) and more attention to bottom–up processes (target stimuli). In other words, the cue's predictive value would change on a trial-by-trial basis. This value would be lower in the IV condition than in the VV condition, consequently producing longer RTs in the former than in the latter. The same concept applies to the comparison of the lower RTs obtained in the VVV condition with respect to the IVV condition. It must be noted that a comparison of the VV and IV conditions would reflect a local effect of the outcome of the previous trial, superimposed on the more robust cost–benefit effect due to global contingencies on the task and the implicit spatial value of the cues [2]. In the same sense, the II trials would be faster than the VI trials because attention would be more related to bottom-up processes in the II condition that in the VI condition.

One central issue pertaining to Bayesian inference is that when a target is encountered, the validity of the prediction (prediction error) must be computed, and the credibility or precision of the hypothesis about where the target should appear as a function of the directional cue must be updated, producing consequences in the next trial. The present results on RTs and errors in dyadic and triadic sequences, with decreased RTs and increased anticipatory errors, and the results from Jongen and Smulders (2007) on RTs in

dyadic sequences, fit the idea of Bayesian inferences during the PCCP. This framework supports the idea that the PCCP is a good example of a cognitive cycle in which preparation for targets, evaluation of trial outcome, and transferring of information from the current trial to the next trial make up a cognitive cycle that facilitates adaptation to environmental cues [29],[10].

Another possible explanation of the sequential validity effect would be in terms of increased strategic or cognitive control in V trials after an I trial occurred, i.e. more cognitive control in IV trials than in VV trials [30], [31]. However this explanation would have difficulties to explain why the II condition is faster than the IV condition. The II<IV result obtained in present report has also been obtained in several reports [8], [12]. In fact, under the cognitive control hypothesis it should be expected the opposite result, more cognitive control after two subsequent Invalid trials (II) than following only one invalid trial (IV condition). The experiments in which increased cognitive control has been proposed to explain longer RTs after incongruent trials had shorter ISIs than the PCCP, and also no cue was interposed between two target stimuli [27,32–35].

The lower RTs and errors in trials preceded by trials with a different auditory stimulus position indicate that an alternation effect [19] appears in this sequence. The lack of interaction between the type of trial (VV, IV, II, and VI) and the position change factor suggests that the expectancy linked to the alternation effect is exclusively based on the position of the previous target. This previous target alternation effect is particularly interesting, given that it operates independently of the type of trial in which it is embedded, and seems to overcome the fact that a directional cue is inserted between the two targets. Given that there are 1900 ms between the current and previous trials, the alternation effect obtained can be included in the type of sequential effects in which the expectancy of next target is computed [20], [18]. This expectancy would follow a rule similar to the gambler's fallacy, where subjects have the tendency to think that the occurrence of a phenomenon makes the occurrence of this same phenomenon less likely in the next trial. For instance, if the previous trial presented a left target, the subject would have a certain tendency to think that the next trial would be right, independently of the type of previous trial. This phenomenon has been studied, the so-called alternation effect, and seems to depend on motor activation as indexed by the Lateralized Readiness Potential [21], [36].

One important consequence of the present results is that this prior can be challenged by experience. In the present experiment, the A-A sequence, which confirms the sequences of alternations, is faster than the R-A sequences in which the sequential repetition-was contradicted in currenttrial [22], [23]. Similarly, the R-R sequence in which the pattern of target location repetitions is confirmed is faster than the A-R in which the sequential alternation is contradicted in current trial. This result implies that the ''gambler's fallacy'' in control subjects without any specific cognitive problems, if an interpretation of this belief as looking for alternation or repetition patterns is done, can be modified by experience in a Bayesian form. Unlike in the present study, Jongen and Smulders (2007) did not find an alternation effect. This difference could be due to the fact that the alternation effect obtained here is rather small, but still statistically significant, probably due to the high number of experimental subjects.

Finally, it should be mentioned that the cost-benefit pattern is induced by the cue [2], but some modulation occurs depending on the history of the sequence in which a given trial is embedded. Basically, this sequence would modulate the preparation for the next trial following (i) a Bayesian rule which updates the credibility of the cue [15,16,9] and (ii) a small influence of the gambler's fallacyprior belief confirmation or disconfirmation. Therefore, confirmatory outcomes in fast reaction times experiments take into account explicit cues (cost-benefit pattern of valid and invalid trials), sequential validity effect(faster if previous trials presented a confirmatory outcome), an alternation effect based on the expectancy that targets different from the previous one are more probable, and the endogenous search for repetitions or alternations patterns. The sequential modulating effects are well explained in the Bayesian brain hypothesis framework [15], [16].

Acknowledgments

The authors would like to thank Cindy de Poy for her English language editorial assistance.

Author Contributions

Conceived and designed the experiments: CMG. Performed the experiments: AA. Analyzed the data: CMG AA. Contributed reagents/materials/analysis tools: AA. Wrote the paper: CMG AA.

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SCIENTIFIC REPORTS

OPEN

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ATTENTION
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Received
19 November 2013

Accepted
11 March 2014

Published
31 March 2014

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Updating of Attentional and Premotor Allocation Resources as function of previous trial outcome

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The neural bases of the inter-trial validity/invalidity sequential effects in a visuo-auditory modified version of the Central Cue Posner's Paradigm (CCPP) are analyzed by means of Early Directing Attention Negativity (EDAN), Contingent Negative Variation (CNV) and Lateralized Readiness Potential (LRP). ERPs results indicated an increase in CNV and LRP in trials preceded by valid trials compared to trials preceded by invalid trials. The CNV and LRP pattern would be highly related to the behavioral pattern of lower RTs and higher number of anticipations in trials preceded by valid with respect to trials preceded by invalid trials. This effect was not preceded by a modulation of the EDAN as a result of the previous trial condition. The results suggest that there is a trial-by-trial dynamic modulation of the attentional system as a function of the validity assigned to the cue, in which conditional probabilities between cue and target are continuously updated.

Organisms must cope with continuous uncertainty between stimuli and outcomes relationships. The Attentional System must deal with this uncertainty and allocate processing resources to guide the organism's actions adaptively. Selective attention allows one to enhance the information received from selected sources and suppress irrelevant, competing sensory inputs[26], increasing signal detectability at attended locations[25]. In a similar manner, the organism must select the more adaptive action between a plethora of simultaneously activated motor programs. The motor attention concept[20,53] has been introduced to indicate that subjects enhance the activity of certain motor programs, in a similar manner as they bias sensory capacities by sensory attention. Motor attention would also be similar to the concept of motor preparation. In the same vein, the so-called 'premotor theory of attention'[48,49] proposes that movements can bias sensory processing to action-compatible percepts. Therefore, sensory and motor attention would be dynamically inter-related.

There is a tendency to approach this phenomenon from a mathematical point of view, taking into account the human capacity to process the probabilities of the occurrence of different events[4,15,46]. Based on these ideas, the present study analyzes the dynamic adjustment of the attentional system in the n trial, given the outcome of the n − 1 trial. The Bayesian Brain Hypothesis about the continuous updating of the prior probabilities in the attentional system[17,60] is applied, hypothesizing that calculating the probability of occurrence of different events guides the attentional resources quickly and accurately to the relevant information and the most likely next scenario. Specifically, this study focuses on the neural mechanisms that are activated when the attention is directed by spatial cues.

The continuous estimate of conditional probabilities between spatial cues and targets[15,22] would facilitate the allocation of attention to the most probable and relevant stimulus. In this view, the attentional system would carry out two parallel processes. On the one hand, it would guide attentional resources, directing them to relevant stimuli. On the other hand, it would continually try to predict the probability of the occurrence of stimuli, based on the subject's previous experience. Friston proposed the 'Bayesian Brain Model' to explain the continuous updating of conditional probabilities between neural representations of sensory stimuli and their external causes[17]. This model includes 'Prediction Error' as the driving force for adaptive changes in synaptic weights, making it possible to modulate the probabilistic relationship between causes and neural representations of causes. Therefore, the dynamic change in the synaptic weights would be due to the effects of neuromodulators, based on the prediction error signal[15,17,22,60].

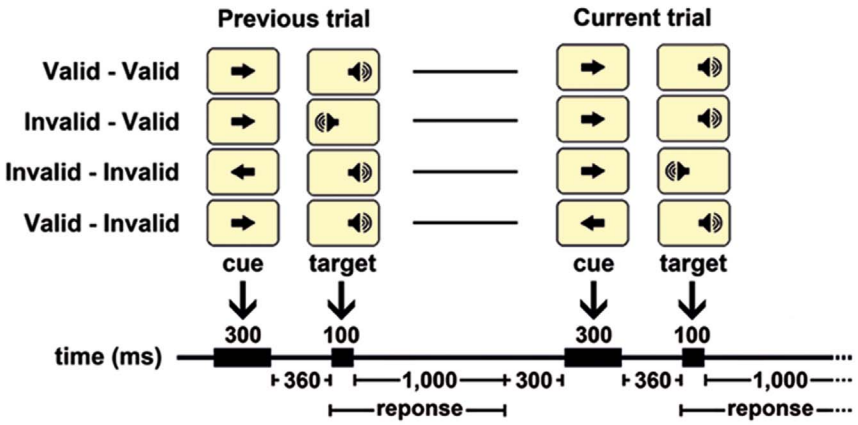

Figure 1 | **Experimental paradigm.** Examples of dyads used in the experiments showing the temporal organization in previous and current trials. The temporal sequence for stimulus presentation appears in the lower part of the figure. The central arrow (cue) was presented in the center of the screen, and the auditory stimulus (target) was presented monoaurally. Behavioral results in dyads were obtained from the signals in the current trial.

The CCPP is an excellent model to test the change in the predictive value of cues as a function of previous trial outcome. This is a classical task used to study the role of resource allocation in visual perception. An initial cue stimulus indicates that a subsequent target stimulus is more likely to appear at the cued location than at other locations[40]. Based on the CCPP, Posner *et al.* proposed an integrative theory of attention in which three different attentional subsystems are present: alert, orientation and executive[42–44]. The use of symbolic cues to predict the appearance of a stimulus in a certain spatial position is related to the pre-activation of the neural resources needed to perceive and respond to the predicted stimulus[10,16,22,27,36]. These predictive neurophysiological signals would be associated with the physiological implementation of the *a priori* probabilities that a target would appear in a certain spatial position. Arjona and Gómez[2] have shown that the Contingent Negative Variation (CNV), induced by the central symbolic cue, modulates its amplitude as a function of the validity of previous trials. Therefore, the CCPP makes it possible to analyze the attentional effects that occur in subjects as a result of the appearance of expected and unexpected stimuli[1,21,28].

The first-order effect in the CCPP correspond to the differences in Reaction Times (RTs) to invalidly and validly cued targets, and would be referred to as the so-called validity/invalidity effect, which is regarded as an indicator of the benefits of being attentionally focused on the location where the stimulus appears, and/or the cost of disengaging and shifting attention from the cued to the uncued location[40,41]. Behavioral studies have shown that the relation of validly to invalidly cued targets influences attentional allocation, with high cue validities increasing the magnitude of the validity effect[29,47,58]. In other words, if the information provided by the cue is highly valid, RTs to valid targets decrease, while reaction times to invalid targets increase.

The second-order effect in the CCPP corresponds to the so-called inter-trial validity-invalidity effect[1,21,28]. This effect would reflect the influence that the assessment of the validity/invalidity in one particular trial (n − 1) has on the next trial (n) performance. These studies have observed benefits in RTs when valid trials are preceded by valid trials (VV), compared to valid trials preceded by invalid trials (IV). Meanwhile, invalid trials preceded by invalid trials (II) reflect a reduction in RTs, compared to invalid trials preceded by valid trials (VI). Therefore, there is a clear trend in RTs between the different trial sequences (VV < IV < II < VI). These findings support the idea that the brain performs a continuous updating of the predictive value assigned to the cue. On a trial-by-trial basis, the brain would be dynamically modulating the attentional system's operation. The credibility assigned to the cue would change with each trial, increasing or decreasing the strength in directing the attentional focus to the indicated place.

Orientation to the cue starts with a posterior negativity contralateral to the location indicated by the cue, the so-called Early Directing-Attention Negativity (EDAN)[27]. During the preparation period, a long-lasting CNV appears with a fronto-central and posterior distribution. The CNV is a signal of negative polarity that appears whenever a subject is expecting the arrival of a significant stimulus in the next few hundreds of milliseconds. It has been observed as an index of different processes such as attention (through the fronto-parietal networks), motor preparation, and sensory activation[5,10,14,22,27,52]. The CNV is related to the preparation of processes necessary for the task. In the case of CCPP, it occurs within the period between the spatial directional cue (S1) and the target stimulus (S2), reflecting the expectation generated by S1 about the appearance of S2[59]. This late negative component increases in trials in which participants invested preparatory effort[12]. In the present study, two periods are analyzed, an initial period called the 'early CNV', which would be related to the sensory orientation process generated by the cue, and a later period called the 'late CNV', which would reflect motor preparation for response to the incoming target[34,51]. Recently, the later period (late CNV) has also been associated with the preparation of the sensory neural areas needed for processing the expected target[5,16,22].

The Lateralized Readiness Potential (LRP) reflects motor activation induced by a warning stimulus. This component is typically observed when subjects make a left-hand response for one stimulus category and a right-hand response for another stimulus category[30]. Initially, the neural activity is equal across both hemispheres, but it rapidly begins to lateralize, with larger amplitudes found in the hemisphere contralateral to the response side and above the motor cortex[11]. Some investigations have successfully employed this component to investigate information transmission between perception and response-related processes[6,22,37].

The purpose of the present study is to examine the neural implementation of the sequential effects in the CCPP, using behavioral results (RTs and Errors) and Event Related Potentials (ERPs), in a visuo-auditory modified version of the CCPP paradigm (Fig. 1). EDAN, CNV and LRP, induced by the cue, are analyzed to understand the neural implementation of the inter-trial validity/invalidity effect. In order to take into account any possible attentional hemispheric lateralization due to the cue direction (left or right), the CNV is analyzed separately as a function of the cue direction. The EDAN and LRP make it possible to assess sensory attentional orientation and motor preparation as a function of previous trial outcome,

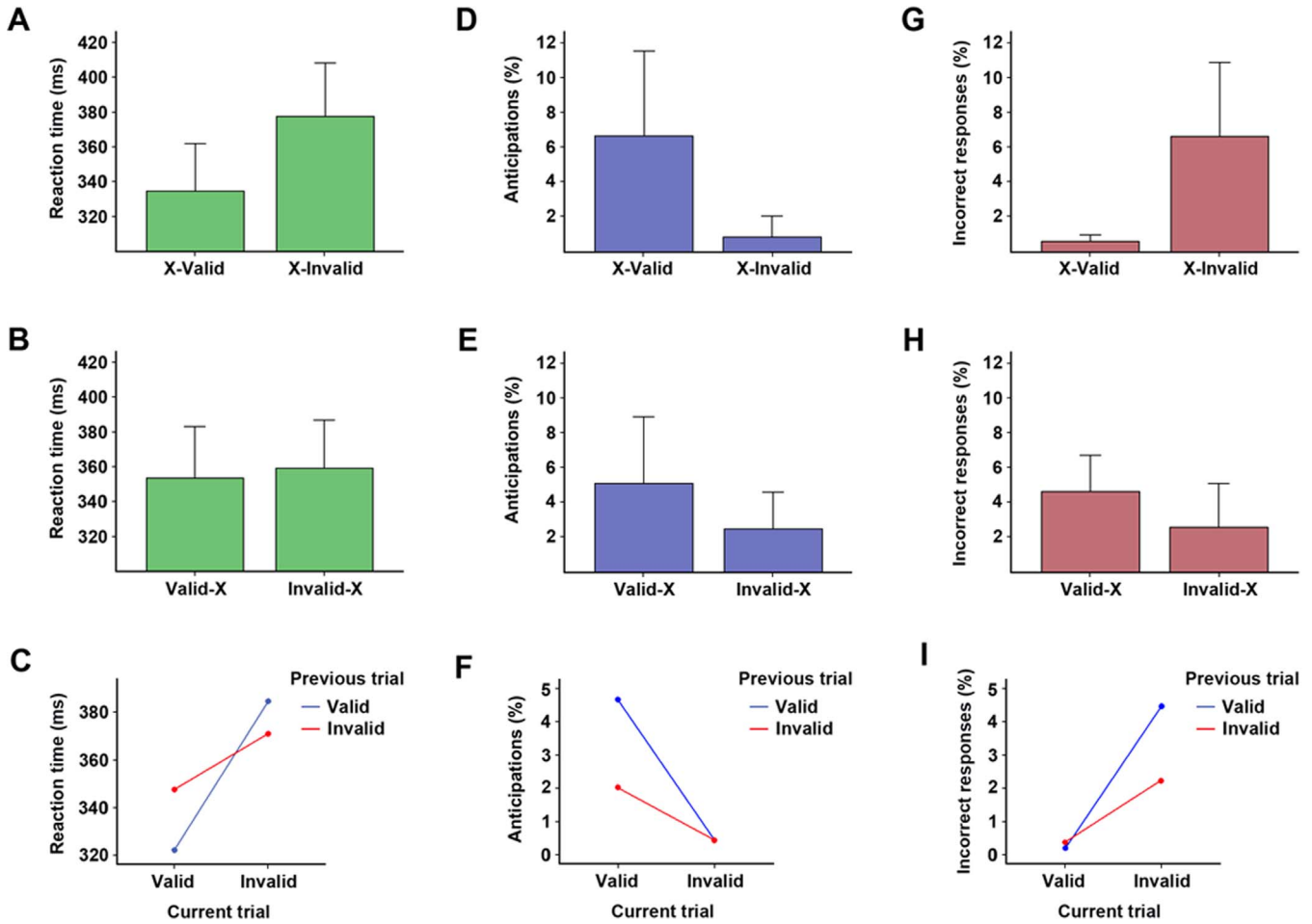

Figure 2 | Comparisons of Reaction times (RTs), Anticipations and Incorrect responses in sequences of two trials (previous and current trial). The 'X' means that the condition of that trial was not taken in consideration. Fig. A shows the mean of RTs in Valid and Invalid trials without taking in consideration previous trial condition. Fig. B shows the mean of RTs in trials preceded by Valid and Invalid trials. Fig. C shows the combined effects of condition (Valid/Invalid) and trial position (current/previous) on the RTs. Figs. D, E and F; and G, H and I illustrate, respectively, the percentage of anticipations and of incorrect responses in the same experimental conditions showed in Figs. A, B and C.

respectively. The objective is to relate the sequential effects in CCPP with preparatory ERPs, considering three types of experimental factors: (i) previous trial condition (valid/invalid); (ii) cue direction in the current trial (left/right); and (iii) current trial condition. The third factor only applies for behavioral responses. Therefore, the following three hypotheses to explain the RTs inter-trial validity/invalidity effect are proposed:

(1) A higher number of anticipations in trials preceded by valid trials compared to trials preceded by invalid trials. This result would indicate an increased preparation induced by the cue as a consequence of validity of previous trial.
(2) The CNV will be more negative in trials preceded by valid trials compared to trials preceded by invalid trials; reflecting higher attentional setting induced by S1 after confirming predictions in the previous trial. As a corollary of this hypothesis, the EDAN components induced by the cue would also be analyzed in order to find out whether invalidity produces a reduction in the visual attentional orientation.
(3) The LRP will present greater amplitude in trials preceded by valid trials compared to trials preceded by invalid trials; reflecting a higher preparation for motor response induced by S1 after confirming predictions in the previous trial.

Note that only inter-trial validity/invalidity effect was analyzed in present report; a detailed analysis of the first-order validity/invalidity effect on ERPs can be found in Arjona and Gómez, 2013[2]. The authors want to state that present results are a reanalysis of previously published data[1,2], in which the inter-trial approach on the EDAN, the LRP and the laterality of the CNV corresponds to new insights of the explanation of the behavioral inter-trial validity/invalidity effect.

Results

All the statistical analyses were performed on the second trial of the two trial sequences (Previous trial – Current trial). The 'X' means that the cue direction (Left/Right) and the condition (Valid/Invalid) of that trial was not considered relevant in those particular trials.

Statistical analysis of reaction times and errors. Reaction times and errors were analyzed by two-factor repeated measures ANOVA in which valid-valid, invalid-valid, invalid-invalid and valid-invalid condition trials were taken into account. Factors were *Previous trial condition* and *Current trial condition*, each one with two valid-invalid levels.

Reaction times. With respect to the *Current trial condition*, RTs in X-Valid were significantly lower than in X-Invalid sequences ($F\ [1, 28] = 56.66$, $p < 0.001$) (Fig. 2A), as expected by the validity/invalidity effect. Furthermore, ANOVA also showed significant differences in RTs with respect to the *Previous trial*

condition (F [1, 28] = 4.67, p < 0.039) due to lower RTs in Valid-X than in Invalid-X sequences (Fig. 2B). Interactions between *Previous trial condition x Current trial condition* were also significant (F [1, 28] = 30.75, p < 0.001) due to a lower RTs in Valid-Valid with respect to Invalid-Valid sequences (p < 0.003) and in Invalid-Invalid with respect to Valid-Invalid sequences (p < 0.054) (Fig. 2C). The lower RTs in Valid-X with respect to Invalid-X sequences and the interactions between the previous and current trial effect (inter-trial validity/invalidity effect) suggest an increased preparation after a valid trial than after an invalid trial.

Three additional analyses on Rts were computed to discard or confirm the possible influence on Rts of the change/repetition of the (i) cue direction (collapsing the four conditions), (ii) target location (collapsing the four conditions) and (iii) cue direction-target location combination in the VV condition. For the cue direction-target location combination only the VV sequence was considered, because in the IV, VI sequences there is always a change in subsequent trials with respect to previous trials, and in the II sequences the division in Change and Repetition would produce very few cases. The mean comparison between Rts in current trials when there was a change or a repetition with respect to previous trials only presented a trend to statistical significance in change/repetition of -target location- (F(1,28) = 3.78, p < 0.062) with a lower Rts for change (339.42 ms) with respect to repetition (344.76 ms).

Errors. Three main types of errors -anticipation, incorrect responses and omissions- were analyzed taken into account the previous and current trial conditions.

For anticipation errors ANOVA showed significant differences in *Current trial condition* (F [1, 28] = 8.01, p < 0.009), due to a higher percentage in X-Valid with respect to X-Invalid sequences (Fig. 2D); in *Previous trial condition* (F [1, 28] = 7.41, p < 0.011), due to a higher percentage in Valid-X with respect to Invalid-X sequences (Fig. 2E); and in *Previous trial condition x Current trial condition* (F [1, 28] = 4.87, p < 0.036), due to a higher percentage in Valid-Valid with respect to Invalid-Valid sequences (p < 0.018) (Fig. 2F).

As in RTs, the effect of the *Current trial condition* in anticipation errors could be related to the validity/invalidity effect in which the anticipatory activity is directed to the target indicated by the cue. The effect of the *Previous trial condition*, with a highest percentage of anticipations in Valid-X than in Invalid-X sequences suggest an increased preparation after a valid trial than after an invalid trial, generating an increased number of endogenously driven responses. The interaction between the previous and current trial effect (*Previous trial condition x Current trial condition*) corresponds to the inter-trial validity/invalidity effect, in which the probability to produce an anticipatory response is increased when previous and current trial are valid.

For incorrect response errors in the *Current trial condition* and also in relation to the validity/invalidity effect, there was a lower percentage in X-Valid with respect to X-Invalid sequences (F [1, 28] = 8.29, p < 0.008) (Fig. 2G). This higher percentage of incorrect responses in X-Invalid suggest that in invalid trials there is an endogenous activity related to the location indicated by the cue inducing incorrect responses. With respect to the *Previous trial condition*, there was a higher percentage of incorrect responses in Valid-X than in Invalid-X sequences (F [1, 28] = 6.23, p < 0.019) (Fig. 2H). The higher percentage of incorrect responses in Valid-X suggest an increased preparation after a valid trial than after an invalid trial, producing more responses to the opposite side of the target location in next invalid trials (Valid-Invalid sequences). In the interaction of the effects *Previous trial condition x Current trial condition,* significant differences were found (F [1, 28] = 42.07, p < 0.004) due to a lower percentage in Invalid-Invalid with respect to Valid-Invalid sequences (p < 0.008) (Fig. 2I). 'Omissions' didn't show significant differences. The interaction between the effects of previous and current trial corresponds to the inter-trial validity/invalidity effect, in which the probability to produce an incorrect response is increased when previous trial is valid (increased preparation to the cue indicated location) and current trial is invalid (target in the opposite side to the indicated location).

Statistical analysis of ERPs. Three post-cue time components induced by the central arrow (EDAN, CNV and LRP) were obtained and statistically analyzed. Two early and late time windows were considered for EDAN (115–155 and 210–325 ms) and CNV (420–520 and 560–660 ms). For LRP, the post-cue time window was 280–660 ms.

Early directing-attention negativity (EDAN). Figures 3A and 3B show the succession of components P1, N1 and P2 generated by the presentation of the central arrow in current trials preceded by valid and/or invalid trials. The ERPs components were generated by spatial orientation of the cue to the left and to the right. These components were more negative over the hemisphere contralateral to the direction indicated by the cue. When ERPs induced by right pointing arrows minus ERPs induced by left pointing arrows were computed, an EDAN component appeared showing an early and a late period (Figs. 3C and 3D).

In the early EDAN, ANOVA showed significant differences for *Hemisphere* (F [1, 57] = 103.42, p < 0.001), *Electrodes* (F [1.68, 95.83] = 5.40, p < 0.009) and *Hemisphere x Electrodes* (F [1.93, 110.31] = 4.45, p < 0.015). In the late EDAN, ANOVA showed statistically differences only for *Hemisphere* (F [1, 57] = 9.73, p < 0.003).

Early and late EDAN did not show significant differences for the factor '*Previous trial condition*'. Instead, the significant differences for *Hemisphere* would indicate the establishing of negativity in the contralateral side to the cue direction. Therefore, results from the EDAN component suggest that there was an orientation related to the cue direction, but that the subsequent modulations of ERP components based on the validity or invalidity of the previous trial seems not to be due to an early sensory attention effect.

Contingent negative variation (CNV). In the early CNV, ANOVA showed significant differences for *Previous trial condition* (F [1, 57] = 14.18, p < 0.001), *Electrodes* (F [2.51, 143.27] = 9.58, p < 0.001) and *Direction of the central arrow in current trial x Hemisphere* (F [1, 57] = 11.74, p < 0.001). In the late CNV significant effects were obtained for *Previous trial condition* (F [1, 57] = 18.08, p < 0.001), *Electrodes* (F [3.02, 172.38] = 11.86, p < 0.001) and *Direction of the central arrow in current trial x Hemisphere* (F [1, 57] = 7.59, p < 0.008). These results indicated that the CNV was of higher amplitude in trials preceded by valid trials compared to trials preceded by invalid trials (Figs. 4A and 4B, left side graphics). In both, early and late periods, the topography of the CNV was fronto-central. The subtraction of 'Invalid-Left cue' and 'Invalid-Right cue' from 'Valid-Left cue' and 'Valid-Right cue' sequences, respectively, revealed a lateralization tendency to the contralateral side of the cue (Figs. 4A and 4B, right side maps), which, as already indicated, was statistically significant (*Direction of the central arrow in current trial x Hemisphere).*

Lateralized readiness potential (LRP). A two-factor repeated-measures ANOVA was performed on the voltage data for three selected pairs of electrodes (F3/F4, FC3/FC4 and C3/C4). ANOVA showed significant differences for *Previous trial condition* (F [1, 57] = 5.57, p < 0.022) due to a higher amplitude of the LRP in trials preceded by valid trials (Valid-X) than in those preceded by invalid trials (Invalid-X) (Figs. 5A, 5B and 5C). This result suggests an increased motor preparation in trials preceded by valid trials than in those preceded by invalid trials.

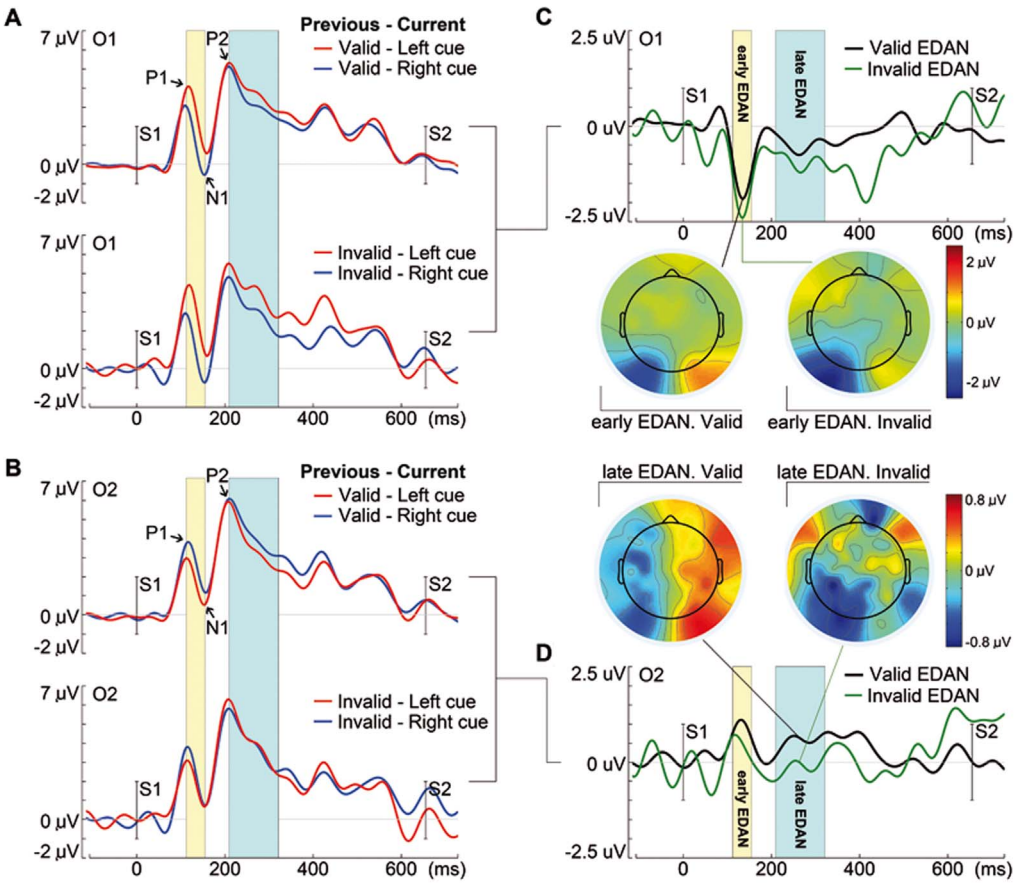

Figure 3 | Effects of the previous valid and invalid trial condition on the Early Directing Attention Negativity (EDAN). Figs. A and B show the Event related potentials induced by the visual cue in current trial after Valid trials (Valid-Left/Right cue) and after Invalid trials (Invalid-Left/Right cue). Figs. C and D show the EDAN waves and topographies generated after Valid and Invalid trials. EDAN was computed by subtracting the ERPs induced by left cues from the ERPs induced by right cues. The shaded areas correspond to the early and late EDAN latencies in which the topographies are represented and where the statistics were computed. The interval −200 to 0 ms before the cue was used as baseline.

Discussion

The present report suggests that attention to spatial cues is continuously modulated as a result of the outcome of the previous trial. CCPP permits the assessment of the deployment of attentional resources needed for responding to a target (S2) validly or invalidly indicated by a previous cue (S1), taking into account the validity or invalidity of the previous trial. The information obtained in each trial would be transmitted to the next trial, producing changes in the processing of the cue, and then influencing the target stimuli processing and the responses (RTs and Errors). The current trial's ERPs modulation by the previous trial would help to explain the inter-trial validity/invalidity effect; lower RTs in trials preceded by valid trials in comparison to trials preceded by invalid trials[1,22,28].

ERPs analysis shows different effects based on previous trial outcome. The CNV shows higher amplitude in trials preceded by valid trials compared to trials preceded by invalid trials, reflecting a dynamic adjustment of attentional resources as a function of previous trial outcome (Fig. 4). The LRP shows higher amplitude in trials preceded by valid trials compared to trials preceded by invalid trials, indicating greater preparation of finger motor areas, generated by the cue, after the confirmation of expectations in the previous valid trial (Fig. 5). The lack of statistically significant effects of the factor '*Previous trial condition*' in the cue-induced EDAN component indicates that inter-trial validity/invalidity effect seems not to be a consequence of an early attentional bias due to the validity or invalidity of the previous trial. The higher LRP amplitude and percentage of anticipations in trials preceded by valid trials in comparison to trials preceded by invalid trials, suggest that the RTs behavioral inter-trial validity/invalidity effect is mostly due to an increased motor attentional setting.

Many studies on the first-order validity/invalidity effect in CCPP have demonstrated that subjects respond faster to targets when they have valid information about the location where they will appear[40]. More recently, inter-trial validity/invalidity effect, in which previous trial outcome influences next trial performance, has been demonstrated[21,28]. The present experiment replicates these findings. One possible explanation for this phenomenon is that previous valid trials increase the credibility of the cue, causing the attentional resources to be more oriented toward the direction indicated by the cue in the next valid trial than in trials preceded by invalid trials, and therefore decreasing response RTs (VV < IV). In contrast, previous invalid trials diminish the credibility of the cue in the next valid trial, reducing attentional orientation to the target location and increasing response RTs. In more formal terms, the conditional probability of a valid 'cue-target' combination would increase after a valid trial. Furthermore, it is noted that invalid trials preceded by invalid trials have lower RTs than invalid trials preceded by valid trials (II < VI); in this case, subjects would pay less attention to and/or assign less credibility to the cue in invalid trials preceded by invalid trials than in invalid trials preceded by valid trials. Therefore, it would take less time to rectify their attentional resources and process the target in the unexpected location. Also, the errors response pattern is consistent with a motor preparation hypothesis; anticipatory and incorrect response errors are more frequent when previous target was validly

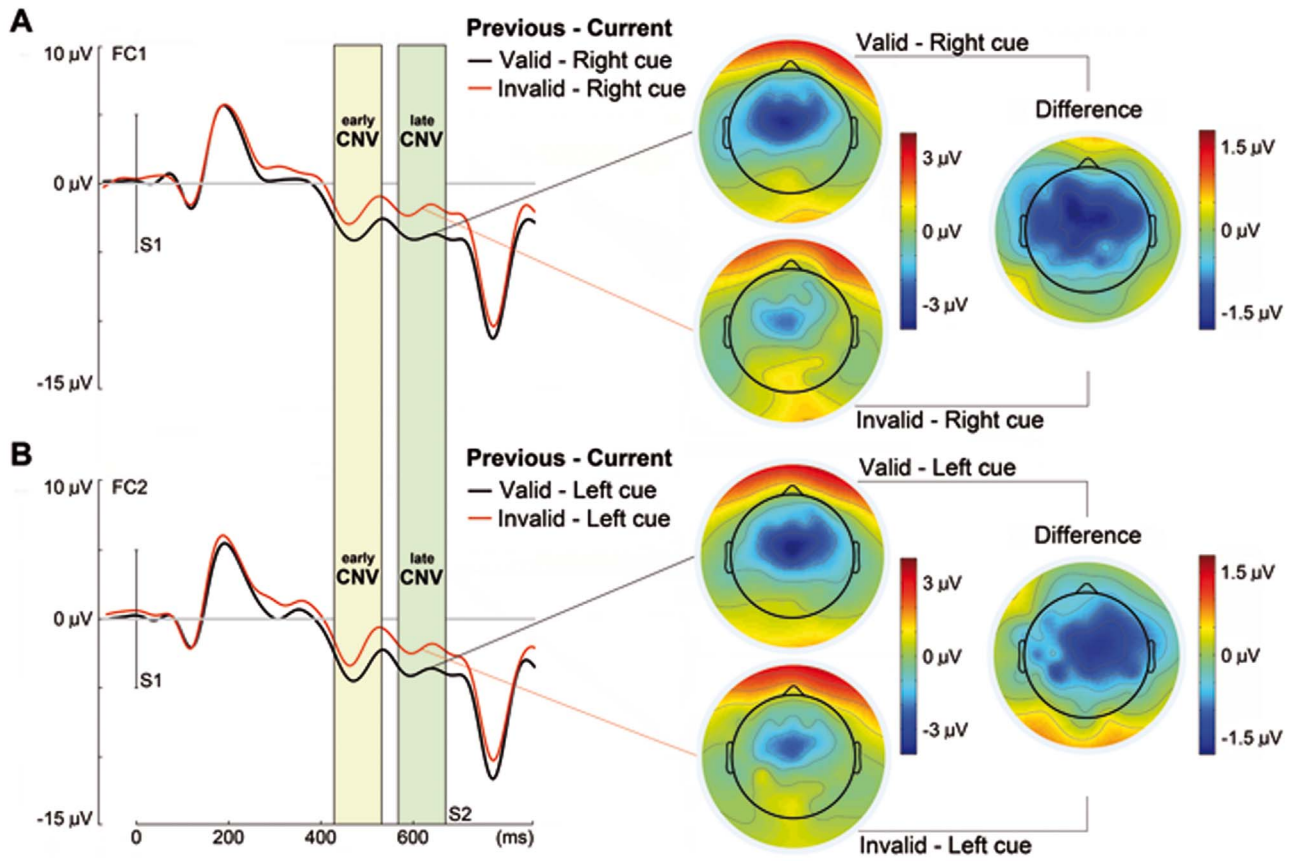

Figure 4 | **Effects of the previous valid and invalid trial condition on the Contingent Negative Variation (CNV).** Figs. A and B show the early and late waves and topographies of the CNV induced by the cue in current trial (Left/Right cue) after Valid and Invalid trials. The CNV displayed a higher negativity, in both hemispheres, in trials preceded by valid trials compared to trials preceded by invalid trials. Also, the topographies indicate that the CNV is contralateral to the cue direction. The shaded areas identify the latencies in which the topographies are represented and where the statistics were computed. The interval −200 to 0 ms before the cue was used as baseline.

cued, suggesting that endogenously driven responses are more frequent if the credibility of the current cue has been increased due to the validity of previous trial.

Additionally, the analyses show that there is no influence of previous trial in terms of equal or different cue direction, target location or cue direction-target location. These results suggest that the 'binding effect' is not related to the sequential validity/invalidity effects in the CCPP[57]. Furthermore, the statistical trend of the factor change/repetition of target location would not have influence on the sequential effect given that change and repetition of target location are equally distributed in VV, VI, IV and II sequences. At this point it would be important to remind that a fundamental difference, that possibly differentiates the sequential effects in CCPP with sequential effects in Stroop, Simon and Flanker paradigms is that in CCPP there is a cue interposed between two target stimuli, which probably induces a different type of phenomena that those induced by successive presentation of target stimuli[3,13,24,33].

From a neurophysiological point of view, previous studies have observed frontal activation related to maintenance of attention during the cue-target delay period, and sensory-motor pre-activation, contralateral to the cue, indicating a build-up of attentional and motor resources necessary to adequately perform the task[16,22,27]. Therefore, the possible modulation of the preparatory signals would be related to the validity/invalidity effect[10,27,36,38,39]. These results are also consistent with the Biased Competition Model[9], which refers to a mechanism that increases the processing of items that are currently relevant to the subject. The attentional system would pre-activate the auditory and motor cortices contralateral to the cue, facilitating target processing. Therefore, in valid trials, attentional resources would be focused on the right place, and take less time to perceive the target and produce the response[22].

The neuronal pre-activation would facilitate perceiving and responding to the target in valid trials. This pre-activation would be dominated by the current value of conditional probabilities between the cue direction and the target location 'P (S2/S1)'. Therefore, the preparatory signals would indicate that subjects are making predictions about the next trial, based on previous trial 'cue-target' associations, and the CNV would be a neurophysiological index of these associations[22].

The behavioral results on the inter-trial validity/invalidity effect suggest that the assessment of the conditional probabilities 'P (S2/S1)' is transferred to the next trial. This idea fits with the Bayesian model of updating the associative weights between cues and targets[17].

The statistical results about the EDAN show that this component seems not to be affected by the condition of previous trial. The absence of this effect would reflect that inter-trial validity/invalidity effect is not a consequence of an early attentional bias due to the validity or invalidity of the previous trial. The attention to the cue is maintained irrespectively of previous trial outcome. However the transfer to the attentional system engaged in the preparation for next cue is biased by result valid/invalid of previous trial.

Present results show that CNV amplitude depends on previous trial outcome[2]. These data, along with the RTs results, support the notion that attention is being modulated trial by trial, based on the previous history of trials. The so-called inter-trial validity/invalidity

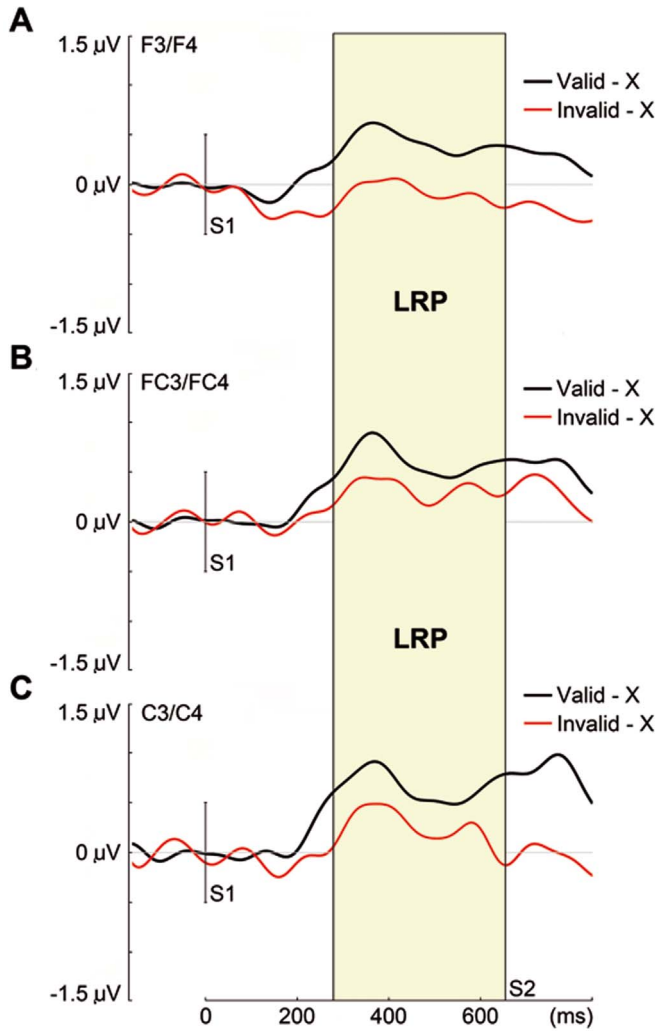

Figure 5 | Effects of the previous valid and invalid trial condition on the Lateralized Readiness Potential (LRP). Figs. A, B and C show the LRP obtained in current trial (X) after Valid and Invalid trials. The 'X' means that the cue direction (Left/Right) and the condition (Valid/Invalid) of current trial were not relevant. The LRP shows higher amplitude in trials preceded by valid trials compared to trials preceded by invalid trials. The shaded area corresponds to the latencies in which the statistic was computed. The interval −200 to 0 ms before the cue was used as baseline.

effect would be reflected in the negative amplitude of the CNV, based on the previous trial condition (Valid/Invalid); trials preceded by valid trials showed higher CNV amplitude compared to trials preceded by invalid trials (Figs. 4A and 4B, left side graphics). These results can be interpreted as a reduction in the expectation and preparation generated by the cue after the previous invalid trial. Instead, previous valid trials would strengthen cue credibility and would produce an increased attention for next indicated target. Topographic analysis shows the increased negativity in fronto-central areas for Valid-Left/Right cue sequences compared to Invalid-Left/Right cue sequences (Figs. 4A and 4B, right side maps), indicating that previous trial validity increases the amplitude of a common network activated in both types of sequences.

It was possible to record a posterior ERP, contralateral to the cue-indicated location, which is compatible in topography and polarity with the EDAN. Although the role of EDAN in analyzing the physical characteristics of the central arrow[56] or indicating attentional orienting[27] is still a subject of controversy, its possible role in attentional orientation has been highlighted[45]. The present results, separating early and late EDAN, would suggest the possibility that both factors (analysis of the physical characteristics of the stimulus and the attentional orienting) would be acting at different latencies. However, for the purposes of the present report, the EDAN seems not to be influenced by the validity or invalidity of the previous trial condition. Therefore, the cue seems to be deeply processed in all trials, but the subsequent deployment of attention (CNV) is the process modified by the inter-trial validity/invalidity effect. It can be suggested that the credibility of the cue must be fully processed to permit the updating of the attentional deployment resources.

CNV amplitude was also measured in two periods (early and late). Both intervals had the same topographic location. This same topography possibly indicates that, given the very short period between S1 and S2, the two CNV periods cannot be easily disentangled in the present experiment. Previous research agrees that the early wave is more related to the salience of the cue value than to response preparation[31,34]. Furthermore, late CNV is assumed to be an indicator of motor and sensory preparation[16,19,51]. CNV activity has been correlated with neuronal activity in the prefrontal cortex[18,50]. This component corresponds to the activation of an attentional fronto-parietal network and sensory-motor areas necessary for the task response[7,22]. The current experiment showed that a valid trial would elicit higher CNV amplitude in the subsequent trial, which is interpreted as an increased attentional deployment of resources. Therefore, the RTs pattern of VV < IV and II < VI would be partly a consequence of the CNV modulation.

In addition to the main '*Previous trial condition*' effect, CNV was contralateral to the cue direction. The LRP is an electrophysiological indicator of neuron pre-activation for motor responses. The present study measured the LRP on fronto-central electrodes (F3 − F4/FC3 − FC4/C3 − C4). The exact locations for obtaining an LRP vary between the different research studies, but central electrodes have frequently been chosen[23,37,54]. This positive wave has one first deflection that is equally large over both hemispheres, but rapidly lateralizes over the motor cortex. This component reflects preparation and initiation of the hand response[32]. Following this line of interpretation, the present experiment would reflect preparation for responses to the side indicated by the cue. In fact, there was increased amplitude of LRP for Valid-X sequences in comparison with Invalid-X sequences (Fig. 5). LRP results are consistent (i) with the benefits on RTs in valid trials preceded by valid trials in comparison with valid trials preceded by invalid trials (VV < IV); and (ii) with the benefits in RTs of invalid trials preceded by invalid trials in comparison with invalid trials preceded by valid trials (II < VI), given that if the previous trial is invalid, less preparation for the invalid response in the current trial occurs, and less reorientation for adequate motor response is needed. The anticipation errors pattern would also be explained by a reduced motor threshold in trials preceded by valid trials in comparison to trials preceded by invalid trials.

It should be mentioned that it is not clear whether LRP and the late phase of CNV reflect similar or functionally different processes[51,55]. In this particular study, LRP might more strictly be described as a lateralized CNV waveform. The different latencies and electrodes used in the analysis of CNV and LRP justify the fact that CNV did not present a '*Previous trial condition x Direction of the central arrow in current trial x Hemisphere*' interaction. Previous MEG studies on visuo-auditory CCPP during the S1–S2 period have shown preparatory activity contralateral to the cue in motor and auditory cortices[22]. However, in the present experiment, using EEG results, it is difficult to disentangle whether the lateralized aspect of CNV, indicated as LRP, is a product of sensory, motor or both processes. Regardless of the origin of the LRP, the influence of previous trial condition on CNV and LRP amplitude suggests a dynamic updating of the credibility assigned to the cue as a function of previous trial outcome, producing the behavioral pattern of the inter-trial validity/invalidity sequential effect.

In summary, the present results show different ERP effects generated by the transfer of information about the outcome of the previous trial to the next trial performance. Specifically, two different ERP components with different functions are modulated as a result of previous trial outcome: (i) the CNV would reflect the dynamic adjustment of attentional resources; and (ii) the LRP would indicate a dynamic adaptation of the pre-activation of finger motor areas, although the modulation of the auditory cortex might also be participating. Possibly, the RTs pattern for VV < IV can be related to the higher motor preparation (LRP) after a valid trial than after an invalid trial. Likewise, the RTs pattern for II < VI would be related to the more intense incorrect motor preparation (LRP) in VI trials with respect to II trials.

In a more general framework, the results indicate that the brain continuously update the conditional probabilities P (S2/S1) as indexed by CNV and LRP modulation by the condition of previous trial. This amplitude modulation of CNV and LRP is compatible with a computational model in which Bayesian rules are implemented in brain networks[17].

Methods

Participants. Thirty-four subjects participated in the experiment. Five subjects with a high number of ocular blinks, EMG and/or trend-derived contaminations in the EEG, were excluded from the analysis. Therefore, data from only twenty-nine subjects (16 female and 13 male) between 19 and 35 years of age (mean: 24 years old and SD: 2.87) were fully analyzed. The experiments were conducted with the informed and written consent of each subject, following the rules of the Helsinki Convention. The Ethics Committee of the University of Seville approved the study.

Stimuli and behavioral paradigm. The stimulus presentation and response recording were computer-controlled (E-Prime 2.0). Participants were seated 60 cm from a computer screen. The subjects participated in a modified version of the CCPP, in which the central cues were arrows appearing in the center of the screen, followed by monoaural auditory stimulation (Fig. 1). The central arrow stimulus was considered the spatial orientation cue (S1), and the monoaural auditory stimulus was the imperative one (S2). The auditory stimuli were delivered to the subject's ears through headphones. Participants were instructed to fixate their eyes on a white cross in the center of the screen and pay attention to the ear indicated by the central arrow. They then had to press the right button as quickly as possible if the auditory stimulus appeared in the right ear, or press the left button if the auditory stimulus appeared in the left ear. The response device was the Cedrus model RB-530. The events sequence within a trial was as follows: the central arrow pointer was on for 300 ms, followed by an expectancy period in which a central fixation white cross appeared for 360 ms. Therefore, the total S1–S2 period was 660 ms. The auditory stimulus (1000 Hz) lasted for 100 ms and was randomly presented to the left or right ear with equal probability (0.5). The stimulus had an intensity of 89 db. The window for the response was 1000 ms, followed by a 300 ms period, producing a total inter-trial interval of 1300 ms (Fig. 1).

Each subject was presented with a total of 500 trials divided into five blocks. The central arrow (S1) had directional information: in half of the trials it pointed to the right, and in the other half to the left. In 80% of the trials the central arrow gave correct information about the target location (V: valid trials), and in 20% of the trials the central arrow pointed to the ear opposite to where the auditory stimulus would appear (I: invalid trials). The cued location (left or right ear) and the trial validity or invalidity, were randomly selected. Therefore, the experiment presented four types of trials: left valid (200 trials), right valid (200 trials), left invalid (50 trials) and right invalid (50 trials). Subjects had to respond to the monaural auditory stimulus with the index finger of the compatible hand. They were informed that the visual cue had informative value, indicating with high probability the location of the auditory stimulus. RTs and percentages of incorrect responses (responses on the side opposite to the stimulated ear), anticipations (responses faster than 180 ms after the onset of auditory target), and omissions (no responses) were computed. The percentage of total errors was computed as the sum of all types of errors. There were ten training trials.

EEG recording, processing and analysis. The EEG was recorded from 64 scalp sites in an extended version of the International 10–20 System, using tin electrodes mounted in an electrode cap (Electrocap). Eye movements (EOG) were recorded from two electrodes at the outer canthus of each eye for horizontal movements, and from one electrode under the left eye for vertical movements, referenced to one electrode above the left eye. Impedance was maintained below 5 KOhms. Data were recorded in DC using a common average as reference, and they were not filtered. Ground electrode was localized in the line between Fpz and Fz. The amplification gain was 20000 (ASA-lab EEG/ERP system, ANT, Holland). The data were acquired at a sampling rate of 256 Hz, using a commercial AD acquisition and analysis board (Eemagine EEG, ANT, Holland).

EEG recordings were analyzed with the EEGlab v10.0.0.0b[8] and Matlab R2010a (MathWorks Inc., MA, USA) software packages. To eliminate AC power line interference and blink artifacts in the EEG, an Independent Components Analysis[35] was performed. Criteria for determining these artifactual components were their scalp map distribution, time course and spectral power. The eye blink artifact component showed a frontal location, coincided with blinking in the recording of eye movements, and showed low frequency in the power spectrum. These components were discarded, and the EEG signal was reconstructed. The segmented epochs had a duration of 2200 ms. Five out of the thirty-four subjects recorded were excluded from the analysis due to a high number of ocular blinks, EMG, and trend-derived contaminations in the EEG.

Artifact corrected recordings were averaged off-line using a rejection protocol based on voltage amplitude. All the epochs for which the EEG exceeded ±90 microvolts in any channel were automatically discarded for ERPs analysis. Moreover, for sequential analysis, the first trial in each block (the experiment had five blocks) had to be rejected because there was no preceding trial. The baseline was the 200–0 ms interval before the cue stimuli. The algebraically-linked mastoids were computed off-line and used as a reference for analytical purposes. ERPs were obtained for each subject by averaging the EEG, using the switching-on of the target as a trigger.

Statistical analysis of RTs, errors and ERPs. Statistical analyses of RTs, Errors and ERPs were performed using repeated-measures ANOVAs. The *P* values were calculated using the Greenhouse-Geisser correction. The very conservative Bonferroni correction for p-values was used to correct statistical significance values for multiple comparisons. The mean voltage in selected time windows was analyzed independently for the different components. Also, the electrode pairs were selected symmetrically in both hemispheres based on previous topography results of every component. All analyses were performed on data extracted from the second trial of sequences of two trials: Previous trial – Current trial.

RTs and Errors ('anticipations', 'incorrect responses' and 'omissions') were analyzed taking into account the condition in previous and current trial. Therefore, four sequences were analyzed by means of a repeated measures two factor ANOVA: valid-valid (VV), invalid-valid (IV), invalid-invalid (II) and valid-invalid (VI). The factors were *Previous trial condition* (2 levels: valid – invalid) and *Current trial condition* (2 levels: valid – invalid).

The mean voltage in the EDAN post-cue time window (Early: 115/155 ms and Late: 210/325 ms) was computed taking into account the condition in previous trial. For computing this component, the ERPs when the arrow pointed to the left was subtracted from the ERPs when the arrow pointed to the right. This arrangement produced negativity in left electrodes and positivity in right electrodes. Trials preceded by valid trials and trials preceded by invalid trials were averaged separately. Electrodes were chosen symmetrically in both hemispheres and compared. These electrode pairs were selected based on previous EDAN topography results (the same criterion was used for the selection of electrodes in the other analyzed components). Therefore, ANOVA was computed with three factors: *Previous trial condition* (2 levels: valid – invalid), *Hemisphere* (2 levels: left – right) and *Electrodes* (PO3/PO4 – PO5/PO6 – O1/O2).

The mean voltage in the CNV post-cue time window (Early: 420/520 ms and Late: 560/660 ms) was computed taking into account the condition in previous trial and the direction of the central arrow in current trial. Electrodes were chosen symmetrically in both hemispheres and compared. Therefore, ANOVA was computed with four factors: *Previous trial condition* (2 levels: valid – invalid), *Direction of the central arrow in current trial* (2 levels: left – right), *Hemisphere* (2 levels: left – right) and *Electrodes* (F1/F2 − F3/F4 − FC1/FC2 − FC3/FC4 − C1/C2 − C3/C4).

The mean voltage in the LRP post-cue time window (280/660 ms) was computed taking into account the condition in previous trial. Three pairs of fronto-central electrodes were chosen and compared. Therefore, ANOVA was performed with two factors: *Previous trial condition* (2 levels: valid – invalid) and *Electrodes* (F3/F4 − FC3/FC4 − C3/C4). The LRP for each type of trial was computed as the mean of the voltage difference between hemispheres when the central arrow pointed to the left and to the right. For instance, to compute the LRP in the Valid-X sequences in C3–C4 electrodes, the following formula was applied to trials preceded by valid trials:

$$((C3-C4)\ \textit{Left arrow}-(C4-C3)\ \textit{Right arrow})/2$$

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Acknowledgments

This work has been possible thanks to grants from the Spanish Ministry of Science and Technology Grant PSI2010-17523 and Ministry of Science and Innovation grant SAF2009-10560 and from the Consejería de Innovación, Ciencia y Empresa of the Junta de Andalucía grant P09-CVI-4712. Co-financed by FEDER founds from the European Union.

Author contributions

A.A. performed the experiment, analyzed the data, designed the figures and wrote the manuscript. G.C. designed the experiment, analyzed the data and wrote the manuscript. E.M. analyzed the data and wrote the manuscript. All authors reviewed and discuss the results and the final manuscript.

Additional information

Competing financial interests: The authors declare no competing financial interests.

How to cite this article: Arjona, A., Escudero, M. & Gómez, C.M. Updating of Attentional and Premotor Allocation Resources as function of previous trial outcome. *Sci. Rep.* **4**, 4526; DOI:10.1038/srep04526 (2014).

Biological Psychology 119 (2016) 171–183

Contents lists available at ScienceDirect

Biological Psychology

journal homepage: www.elsevier.com/locate/biopsycho

Cue validity probability influences neural processing of targets

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ARTICLE INFO

Article history:
Received 8 June 2015
Received in revised form 19 May 2016
Accepted 1 July 2016
Available online 16 July 2016

Keywords:
Posner's paradigm
Attention
Cueing effect
Updating of priors
Validity probability

ABSTRACT

The neural bases of the so-called Spatial Cueing Effect in a visuo-auditory version of the Central Cue Posnerís Paradigm (CCPP) are analyzed by means of behavioral patterns (Reaction Times and Errors) and Event-Related Potentials (ERPs), namely the Contingent Negative Variation (CNV), N1, P2a, P2p, P3a, P3b and Negative Slow Wave (NSW). The present version consisted of three types of trial blocks with different validity/invalidity proportions: 50% valid – 50% invalid trials, 68% valid – 32% invalid trials and 86% valid – 14% invalid trials. Thus, ERPs can be analyzed as the proportion of valid trials per block increases. Behavioral (Reaction Times and Incorrect responses) and ERP (lateralized component of CNV, P2a, P3b and NSW) results showed a spatial cueing effect as the proportion of valid trials per block increased. Results suggest a brain activity modulation related to sensory-motor attention and working memory updating, in order to adapt to external unpredictable contingencies.

1. Introduction

Human beings are immersed in a world of uncertain relationships among stimuli, actions and consequences. The intensity of these relationships needs to be updated in order to improve the adaptive value of responses. Predictions about these relationships make it possible to anticipate the next stimulus and prepare actions. Also, allows to compute the prediction error, which can be considered the driver of the brain network's adaptive changes (Friston, 2009). When people perceive the consequences of their actions, the process of behavioral adaptation begins. Thus, the conduct is immersed in a continuous loop of correction based on previous experience (Fuster, 2004; Gómez & Flores, 2011). This loop can be analyzed through the Central Cue Posner's Paradigm (CCPP) (Posner, 1980). In this experimental paradigm, the subjects (i) generate hypotheses, induced by spatial cues, about the characteristics of the next event in a given context (trying to predict sensory events and prepare adequate motor responses); (ii) perceive the target-stimulus and execute the target-demanded action; and, finally, (iii) confirm or reject their hypotheses, so that their behaviors and underlying neural network connections are fortified or reassessed.

Currently, multiple theoretical approaches include ideas related to this adaptive loop. Fuster (2004) proposed the term "perception-action cycle" to refer to this continuous adaptation of human behavior. It is based on an ongoing assessment of the consequences of actions taken in order to adjust the behavior to the demands of the environment. As Fuster (2008) states, the "perception-action cycle operates at all levels of the central nervous system". Another point of view analyses these adaptive dynamics in terms of probabilities. It is a mathematical approach which considers that subjects generate *a priori* conditional probabilities about the different cues (S1) as predictors of future events (S2). Subjects would change these conditional probabilities (p(S2/S1)) based on the results of previous events (trials in experimental settings), and so the behavior would be continually adapting to the environment (Bruce & Tsotsos, 2009; Feldman & Friston, 2010; Reynolds & Heeger, 2009). In this regard, the model proposed by Friston (2009), known as the 'Bayesian Brain Model', proposes that the brain operates on similar dynamics to the Bayesian Statistics. There would be a continuous change in the conditional probabilities assigned to events based on previous experience. In this context, the concept of 'Prediction Error' would arise as the signal that causes the change in these probabilities, which would correspond, at the neural level, to changes in synaptic weights (Feldman & Friston, 2010; Friston, 2009; Gómez & Flores, 2011). In summary, this model proposes a brain that develops a representation of the world based on the incoming sensory information and the continuous computation of conditional probabilities between world states and neural representations (Knill & Pouget, 2004).

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http://dx.doi.org/10.1016/j.biopsycho.2016.07.001
0301-0511/

One type of stimulus sequence that seems particularly well suited to testing the way cue-target conditional probabilities are updated is the CCPP. In this paradigm, the central cue may validly or invalidly indicate the spatial location of an upcoming target. There are studies showing that the stimuli appearing in attended locations are perceived more easily than the stimuli appearing in unattended locations (Jonides, 1981; Muller & Rabbit, 1989; Posner, Cohen, & Rafal, 1982). When the cue matches the target location (valid trials), faster and more accurate responses are obtained than when they are discordant (invalid trials); this is the so-called 'spatial cueing effect'. This effect shows a Reaction Time (RT) benefit for validly cued targets, and a RT cost for invalidly cued targets. The spatial cueing effect seems to reflect the cost produced by rearranging attentional resources from the side indicated by the cue to the opposite side (Jonides, 1983; Posner, 1980; Posner et al., 1982; Riggio & Kirsner, 1997). The present study aims to analyze this spatial cueing effect from a broader perspective taking in account that cueing not only directs attention to a given location but also defines the probability that the expected event occurs at the cued location (Summerfield & de Lange, 2014). Three types of trial blocks (200 trials per type of block), with different validity/invalidity proportions at the cue-target combination, were analyzed: (i) 50% valid trials – 50% invalid trials, (ii) 68% valid trials – 32% invalid trials and (iii) 86% valid trials – 14% invalid trials (Fig. 1). Thus, it would be possible to observe modulations in subjects' response to the targets based on the higher or lower credibility generated by the cue along each type of block.

From a neural perspective, the objective of the present study was to analyze the ERP amplitude (by means of CNV, lateralized component of CNV, N1, P2 anterior (P2a) and posterior (P2p), P3a/P3b and NSW components) as a result of the credibility generated by the cue along each type of block (50%, 68% and 86% of valid trials). RTs and Errors were also analyzed.

The CNV is a negative slow wave generated by the expectancy of an incoming stimulus (Rockstroh, Elbert, Birbaumer, & Lutzenberge, 1982; Walter, Cooper, Aldridge, & McCallum, 1964). This component has been related to maintenance of attention and/or preparation of motor responses not only for spatial expectancy (Eimer, 1993; Gómez et al., 2004), but also for exogenous (Correa, Lupiáñez, Tudela, & Milliken, 2004, Correa, Lupiaín˜ez, Madrid, & Tudela, 2006; Mento, 2013; Mento, Tarantino, Sarlo, & Bisiacchi, 2013) and endogenous temporal orienting tasks (Mento, 2013; Mento, Tarantino, Vallesi, & Bisiacchi, 2015). Different ERP studies have localized this negativity in fronto-central and posterior sensory areas (Cui et al., 2000; Gómez et al., 2001; Rockstroh et al., 1982; Walter et al., 1964; Zappoli, Versari, & Zappoli, 2000;). Moreover, hemispheric asymmetry of this slow wave has been reported under conditions of motor preparation, anticipation and in sensorial tasks (Butler & Glass, 1974; Kutas & Donchin, 1980; Lutzenberger, Elbert, Rockstroh, & Birbaumer, 1985; McCarthy & Donchin, 1978).

Previous studies, using similar tasks to present report, have observed sensory-motor pre-activation indexed by the CNV, which would reflect the build-up of the resources necessary for the adequate performance of the task (Butler & Glass, 1974; Brunia & Van Boxtel, 2001; Flores, Digiacomo, Meneres, Trigo, & Gómez, 2009; Gómez et al., 2001, 2003; Kutas & Donchin, 1980; Mento, 2013; Mento et al., 2013). The sensory-motor pre-activation produces a benefit in perceiving and responding to the targets in valid trials, and it would be influenced by the processing of S1–S2 probabilities in previous trials (Arjona & Gómez, 2013). This idea fits the Bayesian model of learning as the modulation of associative weights between cues and targets (Feldman & Friston, 2010; Friston, 2009; Gómez & Flores, 2011; Waldmann & Martignon, 1998). With regard to the hypotheses of present report, if CNV is related to expectation, its amplitude must increase in the contralateral side to the cued location as a function of cue validity, and would reflect baseline shifts to the expected stimulus (Summerfield & de Lange, 2014). In this sense, the relationship of CNV with expectation of global sequences (Chennu et al., 2013), and with targets in CCPP (Arjona et al., 2014), has been previously reported.

In CCPP, the target stimulus is followed by a series of ERPs. The 'predictive coding hypotheses' propose that ERP amplitudes to validly cued stimuli must be smaller in comparison to invalidly cued stimuli, not only because expected stimuli would not produce the prediction error generated by invalidly cued stimuli, but also because validly cued stimuli would benefit the sharpening of the tuning curves of sensory neurons, similarly to the suppression repetition effect (Summerfield & de Lange, 2014). In the context of present report, previous hypothesis would predict that the neural response difference between invalidly and validly cued targets must increase (invalid > valid) with the increase of the block cue-validity, given that invalid targets would produce a higher prediction error as the valid proportion of trials per block increases. In this line, with regard to early ERP components (N1 and P2), there may be also an influence in the opposite direction (valid > invalid), given that increased predictability should increase attention to the cued location and would produce the increase of activity to attended stimuli (Hillyard, Hink, Schwent, & Picton, 1973). Therefore, it is possible that, at least for early ERP components, a weighing of the opposite effects of prediction and attention is occurring (Lange, 2013). Instead, in late ERP components (P3a, P3b and NSW), attentional effects should be synergistic with prediction effects (Chennu et al., 2013), and the assessment of adequacy between predicted and current target location would induce increased amplitude in invalid trials with respect to valid trials.

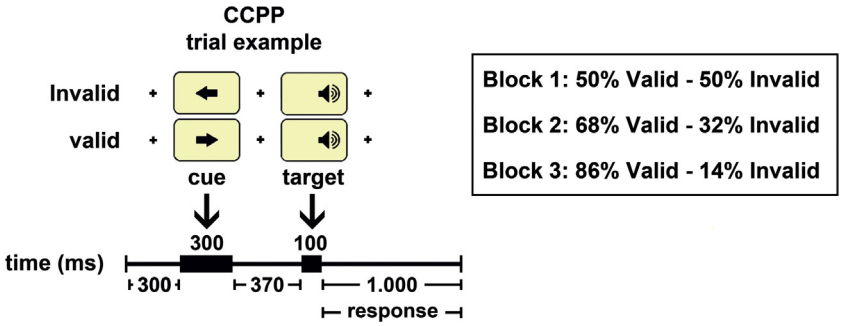

Fig. 1. Experimental paradigm. Trial example (valid and invalid) used in the experiment. The temporal sequence for stimulus presentation appears in the lower part. The central arrow (cue) was presented at the center of the screen, and the auditory stimulus (target) was monaurally emitted through the headphones. On the right side a box appears with the validity/invalidity proportion of trials for each block.

Auditory targets elicit N1 components with a negative polarity. This component has peak latency around 100 ms after the target stimulus and is maximally recorded at the fronto-central area. Previous studies indicate that may reflect the distribution or allocation of the subjectís attention (Woldorff, Gallen, Hampson, Hillyard, & Pantev, 1993; Woldorff & Hillyard, 1991). Hillyard et al. (1973) proposed that N1 shows increased potential (elicited by selective attention) when auditory stimuli appear in random order through different sensory channels (such as the two ears) and the subject pays attention to one channel. Näätänen, Gaillard, and Mäntysalo (1978) have dissociated this negative ERP between the N1 component and an overlapping attention-related wave called 'Processing Negativity (PN)' that occurs during the N1 latency range. Different studies show that N1 is an early auditory component significantly determined by the characteristics of the incoming target (Huotilainen et al., 1998; Woldorff et al., 1993). The review of Summerfield and de Lange (2014), shows that N1 amplitude is not only increased by attention, as obtained in filtering paradigms (attending to one ear), but it is also reduced when target prediction is increased. This reduction of N1 amplitude to predictable auditory stimuli has been repeatedly obtained in experiments in which the auditory stimulus is triggered by the own's one motor action or by temporally predictable auditory stimuli. Therefore, the weighing of prediction and attention would possibly produce null effects on N1 amplitude in CCPP.

Auditory targets also elicit P2 components with central-posterior topography (Crowley & Colrain, 2004). P2 is a medium-latency component that occurs around 200 ms after the relevant stimuli and co-varies with N1 across many stimulus dimensions. However, this wave has been dissociated as an independent component in different studies (Ford, Roth, & Kopell, 1976; Oades, Dittman-Balcar, & Zerbin, 1997; Vaughan, Ritter, & Simson, 1980). In the auditory modality, has been indicated that attended stimuli elicit enhanced N1 and P2 components compared to unattended stimuli, causing these components to be interpreted as correlate of mechanisms that improve the processing of attended stimuli (Arjona & Gómez, 2013; Näätänen, 1992; Woldorff & Hillyard, 1991). Nevertheless, Golob, Pratt, and Starr (2002) showed larger N1 and P2 components elicited by invalidly cued targets. Regard to present report, an increase of anterior P2, correlative to the increase of the proportion of valid trials per block, must be expected if the component is driven by attention. Instead, a null effect is expected if prediction and attention are weighing their effects (Summerfield & de Lange, 2014). The posterior face of P2 will also be analyzed, being particularly relevant for supporting hierarchical models of prior probability updating. This concept imply that posterior visual areas should be modulated by prediction error in order to update the P(S2/S1) at early processing stages.

Finally, it has been suggested that the failed subjective expectancy induced by the cue in invalid trials causes an increased P300, which reflects attentional automatic orientation (P3a) and conditional probabilities updating (P3b) about the cue-target combination (Arjona & Gómez, 2013; Eimer, 1993; Golob et al., 2002; Gómez, Flores, Digiacomo, Ledesma, & González-Rosa, 2008, Gómez, Flores, Digiacomo, & Vázquez-Marrufo, 2009; Gómez & Flores, 2011; Mangun & Hillyard, 1991). Regarding P3b, Donchin and Coles (1988) proposed that P3b would represent a context-updating operation and the subsequent memory storage; Verleger, Jaskowski, and Wascher (2005) suggested that P3b is related to the neural linkage between stimulus perception and the response to that stimulus; and Polich (2007) showed that the P3b component is related to the neuroinhibition needed to focus attention on the relevant task, facilitating the interference-free action of memory systems. This parieto-occipital component has also been suggested to indicate an assessment of the absence of adequacy between sensory-motor preparation and sensory perception in working memory, for both the auditory (Arjona & Gómez, 2013; Golob et al., 2002) and visual modalities (Gómez et al., 2008; Mangun & Hillyard, 1991), in CCPP. The P3 component has also been related to the Bayesian inference (Chennu et al., 2013; Friston, 2005; Kopp, 2008). In the context of present report, the P3a and P3b modulation should increase in the invalid trials as the percentage of valid trials per block increases (Condition × block effect). In this line, the amplitude of CNV has been related to the activation of the neural set needed for processing the next target (Gómez et al., 2001), and to the credibility assigned to the cue (Arjona et al., 2014; Chennu et al., 2013); therefore, it is probable that some sort of quantitative relationship exists between the amplitude of CNV and the modulation of P3b in the invalid trials.

Furthermore, a frontal negativity around the P3b latency, the NSW, has been described in the auditory modality as a response to distractors. This ERP has been suggested that represents the reorientation effort after distracters or the so-called reorientation negativity (Wetzel & Schröger, 2014). In present study, this negativity is expected to be present in invalid trials, due to the reorientation effort produced by the invalidly cued target.

In sum, the present study shows the influence of the validity/invalidity proportion of trials per block on behavior and on cognitive operations. ERPs were divided into pre-target (CNV and lateralized component of CNV) and post-target (N1, P2a, P2p, P3a, P3b and NSW). Based on this arrangement, there were several hypotheses to test: **(1)** the CNV amplitude will be greater as the proportion of valid trials per block increases, showing higher sensory-motor preparation; **(2)** the N1 and P2a amplitude will be greater on valid trials, compared to invalid trials, as the proportion of valid trials per block increases, reflecting higher attentional modulation produced by the expected target; **(2b)** alternatively, N1 and P2 components will not present amplitude modulation on valid trials generated by these increase of the cue validity per block, due to a weighing of opposite effects of attention and prediction; **(3)** P2p, P3a and P3b amplitude will be higher on invalid trials, compared to valid trials, as the proportion of valid trials per block increases, indicating an effort for attentional reorientation and working memory updating generated by the unexpected target. Working memory updating must be understood as the mechanism changing the p(S2/S1) (or in the context of CCPP paradigms p(target/cue)). In this line, if P3b is related to the assessment of the unexpectedness of an invalid target (in other words the amplitude of the prediction error), there must be a correlation between the amplitude of CNV (indexing the *a priori* validity probability) and the modulation by invalidity of the P3b, indexing the discrepancy between predicted location (with a certain validity) and the current position of the target. Therefore, as a corollary of hypotheses (1) and (3), a significant correlation between CNV amplitude and P3b amplitude is expected if sensory-motor preparation (CNV) is related to p(S2/S1) updating (P3b modulation by invalid cues); and **(4)** the NSW will have a higher amplitude in invalid trials, compared to valid trials, as the proportion of valid trials per block increases, due to a higher attentional demand to reorient attention, and/or a higher alerting after low probability invalid targets.

2. Results

2.1. Analysis of reaction times and errors

2.1.1. Reaction times

ANOVAs of RTs were computed considering two factors: *Condition* (valid, invalid) and *Block* (50%, 68%, 86% of validity proportion).

For the RTs (Fig. 2A), ANOVA showed significant differences in *Condition* ($F[1, 29] = 67.68$, $p < 0.001$, $\eta_p^2 = 0.70$), due to faster RTs in the valid trials compared to invalid trials, as expected by

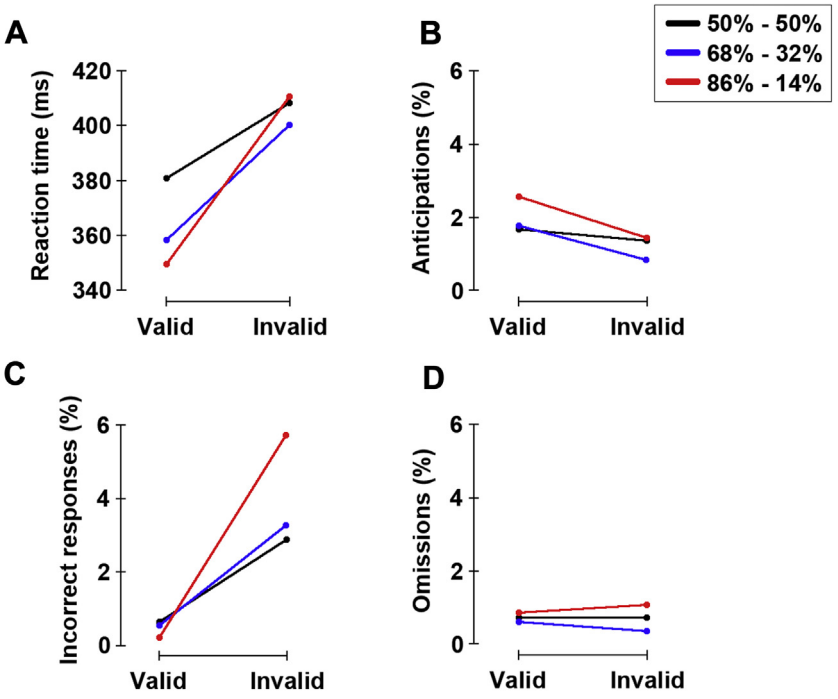

Fig. 2. Comparisons of Reaction Times (RTs), Anticipations, Incorrect responses and Omissions in valid/invalid trials, within the three types of blocks. Fig. 2A shows the RTs mean in valid/invalid trials within the three types of blocks. Note the greater difference between conditions as the percentage of valid trials per block increases. Fig. 2B shows the percentage of Anticipation errors in valid/invalid trials within the three types of blocks. Fig. 2C shows the percentage of Incorrect response errors in valid/invalid trials within the three types of blocks. Note the greater difference between conditions as the percentage of valid trials per block increases. Fig. 2D shows the percentage of Omission errors in valid/invalid trials within the three types of blocks.

the spatial cueing effect in CCPP; and *Condition* × *Block* ($F\,[1.71, 49.80] = 22.59$, $p < 0.001$, $\eta_p^2 = 0.43$), due to a higher RTs difference (invalid minus valid) as the proportion of valid trials per block increases. The Bonferroni comparisons were applied to previous interaction (subtracting the RTs of valid from invalid trials) and significant differences were obtained: 86% > 68% ($p < 0.003$), 86% > 50% ($p < 0.003$) and 68% > 50% ($p < 0.003$). This interaction effect indicates that there is a higher RTs difference (invalid vs valid) as the proportion of valid trials per block increases.

2.1.2. Errors

Anticipation, Incorrect response and Omission errors were independently analyzed. The Shapiro-Wilk test of normality showed that the data set were not normally distributed for any error variable.

For Anticipation errors (Fig. 2B) the Wilcoxon Signed-Ranks test indicated that the percentage of anticipations was significantly higher in valid trials, compared to invalid trials, only in the block of 68% ($Z = -2.7$, $p < 0.007$). In sum, these results showed that there were not consistent significant effects for Anticipation errors related to the percentage of validity per block.

For Incorrect response errors (Fig. 2C) the Wilcoxon Signed-Ranks test indicated that the percentage of incorrect responses was significantly higher in the invalid condition, compared to the valid condition, in the block of 50% ($Z = -2.96$, $p < 0.003$), 68% ($Z = -3.92$, $p < 0.001$) and 86% ($Z = -3.6$, $p < 0.001$). Additionally, the Wilcoxon Signed-Ranks test showed that the difference between conditions was significantly higher in the block of 86% compared to 50% ($Z = -3.02$, $p < 0.002$) and 68% ($Z = -2.86$, $p < 0.004$).

The percentage of Omission errors (Fig. 2D) was very small and showed no significant differences.

2.2. Analysis of event related potentials

After the visual exploration of ERPs, the CNV component, induced by the central arrow, and six components observed after the auditory target (N1, P2a, P2p, P3a, P3b and NSW) were analyzed. The electrodes in each component (except P2p and the NSW) were selected based on previous studies (Arjona, Escudero, & Gómez, 2014; Arjona & Gómez, 2013) using a similar CCPP paradigm.

2.2.1. Contingent negative variation (Central)

The CNV (Supplementary Fig. S1 in the online version at DOI: 10.1016/j.biopsycho.2016.07.001) presented a fronto-central distribution. A two-factors repeated measures ANOVA was performed on the voltage data of the CNV time window (370–670 ms after the cue arrow). Factors were: *Block* (50%, 68%, 86%) and *Electrode* (Fz, Cz). The ANOVA showed no significant differences for any factor. This result indicates that there were not significant differences in the central area of the CNV generated by the different proportions of validity/invalidity per block.

2.2.2. Lateralized component of CNV

An analysis of the CNV time window was recorded in the lateral electrodes (Fig. 3). The voltage data was computed as indicated in the 'Materials and Methods' section. The lateralized component of CNV would make it possible to observe hemispheric differences in the CNV period induced by the cue direction. A two-factors repeated measures ANOVA was performed on the voltage data of the CNV time window. Factors were: *Block* (50%, 68%, 86%) and *Couple of Electrodes* (F3/F4, FC1/FC2). ANOVA showed a tendency to significant differences in *Block* ($F\,[1.93, 56.10] = 3.01$, $p < 0.059$, $\eta_p^2 = 0.09$). The Bonferroni comparisons were applied to this factor and showed significant differences: 86%>50% ($p < 0.048$). This result suggests higher sensory-motor preparation to respond as the proportion of valid trials per block increases.

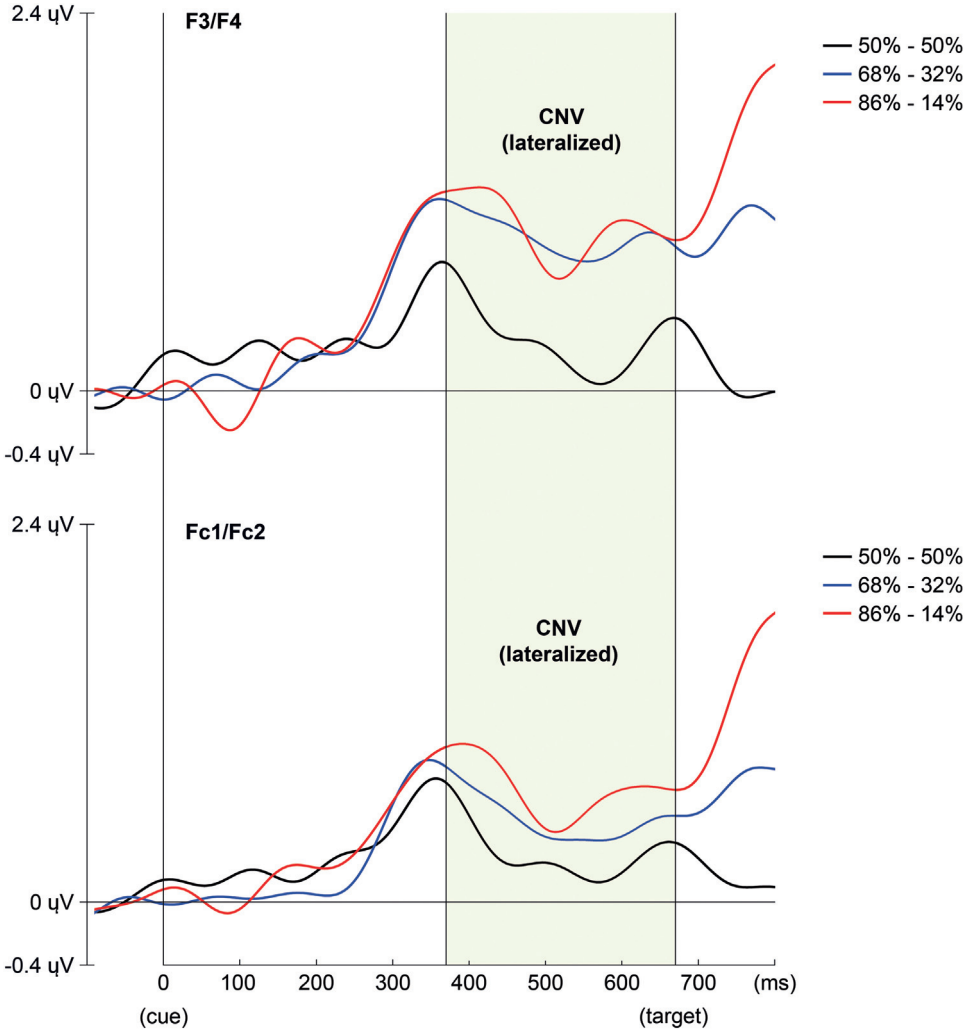

Fig. 3. Effects of the type of block on the lateralized component of CNV. The panel shows amplitude of the lateralized component of CNV induced by the three types of blocks. Note the trend toward higher positivity as the proportion of valid trials per block increases.

Complementary, the equation permitting to compute the lateralized component of CNV was also applied to the voltage data of the electrodes recording the horizontal eye movements (Supplementary Fig. S2 in the online version at DOI: 10.1016/j.biopsycho.2016.07.001). A one-factor ANOVA (Block (50%, 68%, 86%)) was computed in order to check whether the significant effects of the type of block on the lateralized component of CNV were due to eye movements. Results showed no significant differences, indicating that the block effect on the lateralized component of CNV was not due to eye movements.

2.2.3. N1 component

The N1 component was located in fronto-central areas (Figs. 4 and 5). A three-factors repeated measures ANOVA was performed on the voltage data of the N1 time window (90–120 ms after the auditory target). Factors were: *Condition* (valid, invalid), *Block* (50%, 68%, 86%) and *Electrode* (FC1, FC2, C3, Cz, C4). ANOVA showed significant differences in *Electrode* ($F\,[3.09, 89.68] = 9.86$, $p < 0.001$, $\eta_p^2 = 0.25$); *Condition* × *Block* ($F\,[1.92, 55.92] = 3.48$, $p < 0.039$, $\eta_p^2 = 0.10$); and *Condition* × *Electrode* ($F\,[2.72, 78.87] = 5.36$, $p < 0.003$, $\eta_p^2 = 0.15$). The Bonferroni comparisons were applied to the interaction *Condition* × *Block* showing not significant differences. However, if no multiple comparisons are taken into account, there was a significant difference in 86% > 68% ($p < 0.020$) (Fig. 6A). These results indicate that there was a tendency to higher amplitude of the N1 component in valid trials, compared to invalid trials, as the proportion of valid trials per block increases (Fig. 6A).

2.2.4. P2 component

The P2 component showed a central-posterior topography, in both valid and invalid conditions, that was stronger in the invalid condition (Fig. 5). In the difference topography (subtracting ERPs in the invalid condition from ERPs in the valid condition), an anterior positive topography (P2a) and a posterior negative topography (P2p) emerge as validity increases (Figs. 4 and 5).

A three-factors repeated measures ANOVA was performed on the voltage data of the P2a time window (153–193 ms after the auditory target). Factors were: *Condition* (valid, invalid), *Block* (50%, 68%, 86%) and *Electrode* (F3, Fz, F4, FC1, FC2). ANOVA showed significant differences in *Block* ($F\,[1.88, 54.59] = 4.05$, $p < 0.025$, $\eta_p^2 = 0.12$); *Electrode* ($F\,[1.89, 55.08] = 26.29$, $p < 0.001$, $\eta_p^2 = 0.47$); *Condition* × *Block* ($F\,[1.97, 57.29] = 3.37$, $p < 0.042$, $\eta_p^2 = 0.10$); *Condition* × *Electrode* ($F\,[2,58.09] = 10.76$, $p < 0.001$, $\eta_p^2 = 0.27$); *Block* × *Electrode* ($F\,[4.16, 120.73] = 7.77$, $p < 0.001$, $\eta_p^2 = 0.21$); and *Condition* × *Block* × *Electrode* ($F\,[4.14, 120.27] = 5.47$, $p < 0.001$, $\eta_p^2 = 0.15$). The Bonferroni comparisons were applied to the interaction *Condition* × *Block* showing significant differences: 86% > 50% ($p < 0.036$) and 68% > 50% ($p < 0.030$).

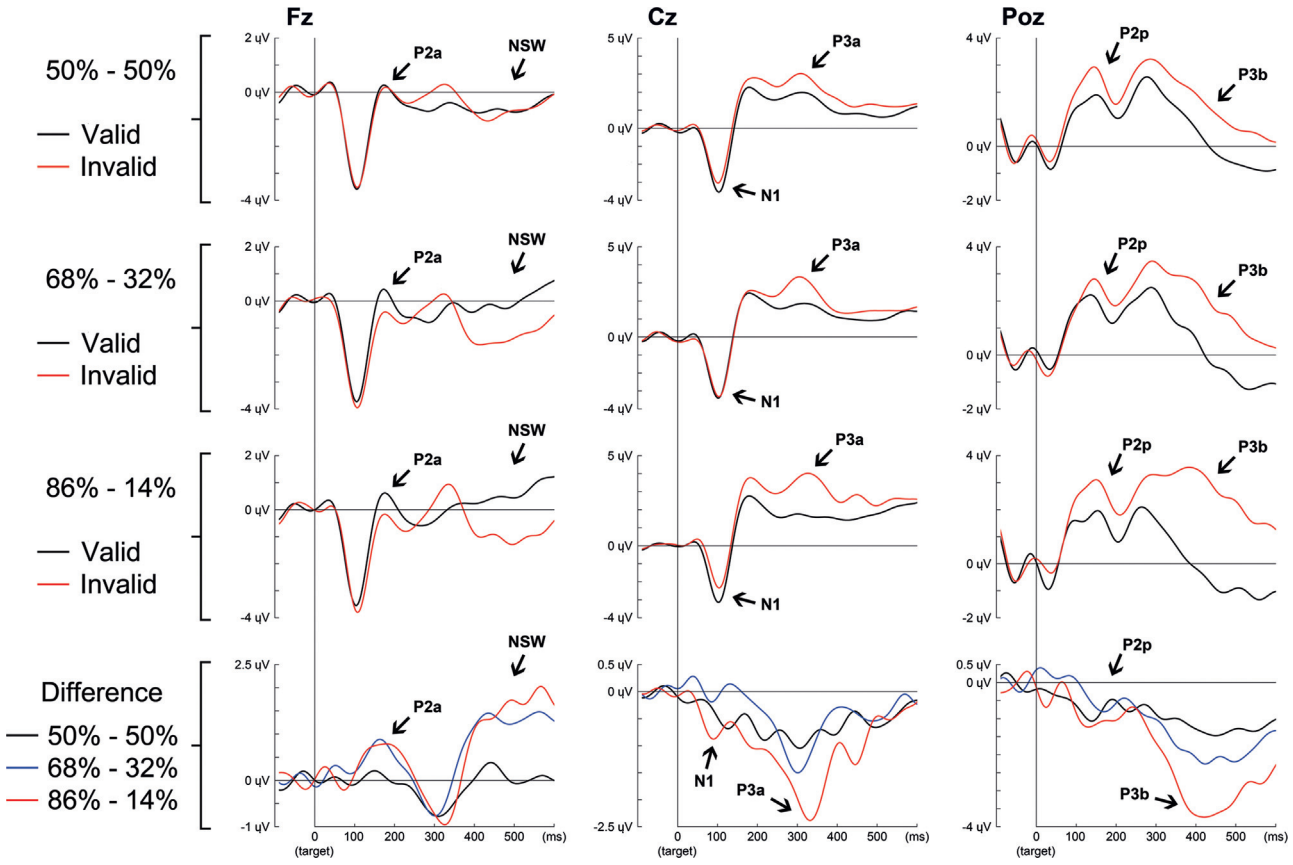

Fig. 4. Post-target ERPs (N1, P2a, P2p, P3a, P3b and NSW) in valid/invalid trials and difference waves (valid minus invalid), within the three types of blocks. The block type is indicated on the left side: *50%*, *68%*, *86%* and *block difference* (from top to the bottom). Three midline electrodes are represented from left to right (*Fz*, *Cz* and *Poz*). The different components are identified within the graphics: P2a and NSW (*Fz*); N1 and P3a (*Cz*); P2p and P3b (*Poz*). Note that: (i) the N1 and P2a amplitudes are higher in valid trials than in invalid trials; and (ii) the P2p, P3a, P3b and NSW amplitudes are higher in invalid trials than in valid trials.

A three-factors repeated measures ANOVA was performed on the voltage data of the P2p time window (153–193 ms after the auditory target). Factors were: *Condition* (valid, invalid), *Block* (50%, 68%, 86%) and *Electrode* (CP1, CP2, P3, Pz, P4). ANOVA showed significant differences in *Condition* ($F\ [1, 29] = 20.29$, $p < 0.001$, $\eta_p^2 = 0.41$), due to higher positivity in the invalid condition with respect to the valid condition; *Electrode* ($F\ [1.55, 44.95] = 9.40$, $p < 0.001$, $\eta_p^2 = 0.24$); and *Condition* × *Electrode* ($F\ [2.97, 86.21] = 3.52$, $p < 0.019$, $\eta_p^2 = 0.10$).

P2 results show an increase in P2a amplitude as the proportion of valid trials per block increases (Fig. 6B). Instead, the P2p component was affected by the trial condition (valid/invalid), but the effects of the interaction between the condition and the type of block were not significant (Fig. 6C).

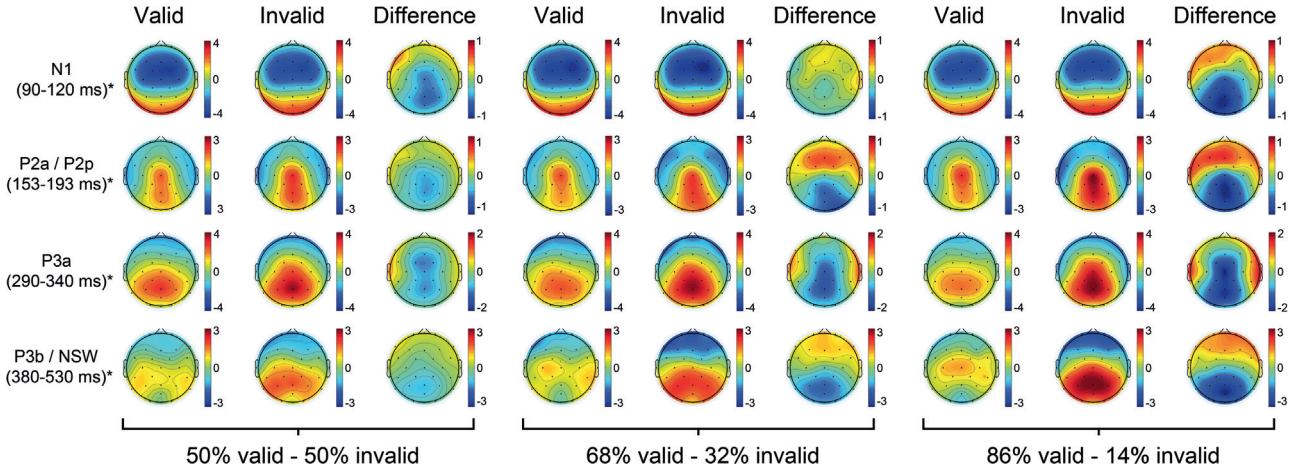

Fig. 5. Topographical maps of post-target ERPs (N1, P2a, P2p, P3a, P3b and NSW) in valid/invalid trials and differences (valid minus invalid), within the three types of blocks. The block type is indicated at the bottom of the figure: *50%*, *68%* and *86%*. Components are identified on the left side: *N1*, *P2a/P2p*, *P3a* and *NSW/P3b* (from top to bottom). The valid/invalid conditions with their differences (indicated on top) within the three types of blocks (indicated at the bottom) are represented from left to right. Note the greater difference between conditions, for most components, as the proportion of valid trials per block increases.

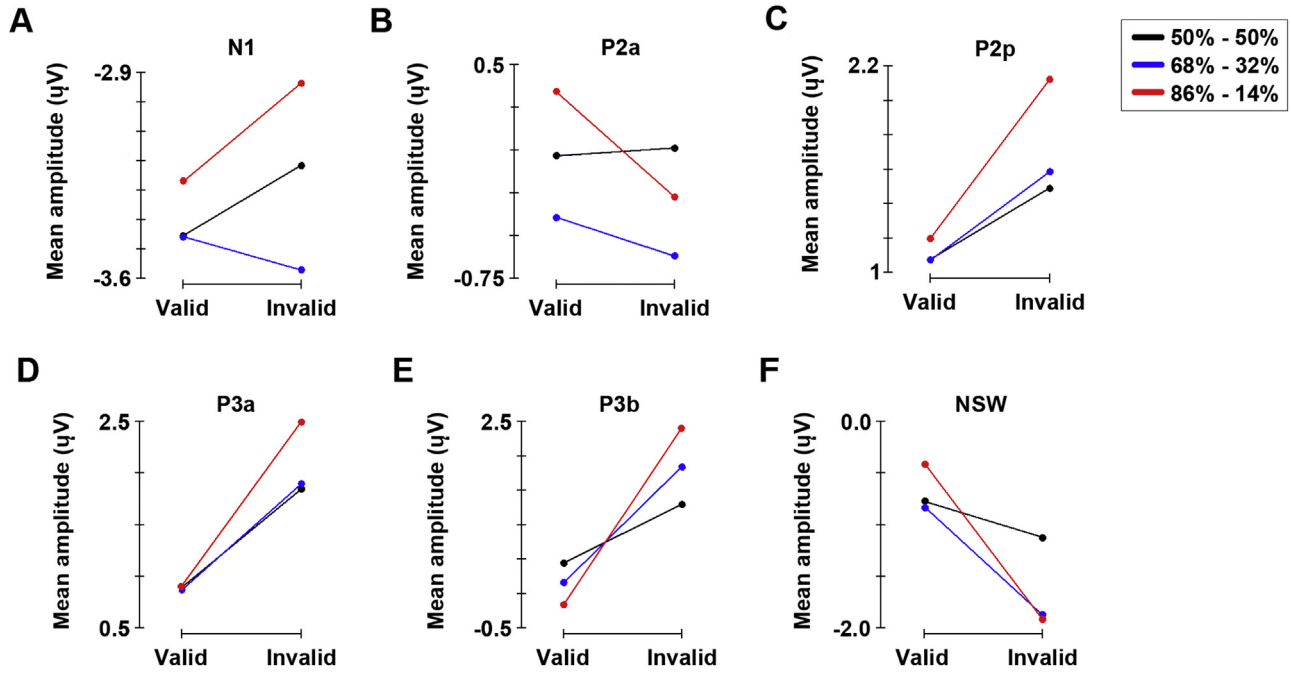

Fig. 6. Mean amplitude of the post-target ERPs (N1, P2a, P2p, P3a, P3b and NSW) in the valid/invalid conditions, within the three types of blocks. Fig. 6A shows the N1 mean amplitude (electrodes FC1, FC2, C3, Cz and C4). Fig. 6B shows the P2a mean amplitude (electrodes F3, Fz, F4, FC1 and FC2). Note the greater difference between conditions (valid/invalid) for N1 and P2a within the 86% block. Fig. 6C shows the P2p mean amplitude (electrodes CP1, CP2, P3, Pz and P4). Fig. 6D shows the P3a mean amplitude (electrodes FC1, FC2 and Cz). Fig. 6E shows the P3b mean amplitude (electrodes P3, Pz, P4, POz, O1, Oz and O2). *Fig. F* shows the NSW mean amplitude (electrodes FP1, FPz, FP2, F3, Fz and F4).

2.2.5. P3 component

The P3 component shows a posterior positivity that extended to central regions in the invalid condition (Fig. 5). However, when the difference wave was obtained, an early central positivity (P3a) and a late posterior positivity (P3b) appeared (Figs. 4 and 5).

A three-factors repeated measures ANOVA was performed on the voltage data of the P3a time window (290–340 ms after the auditory target). Factors were: *Condition* (valid, invalid), *Block* (50%, 68%, 86%) and *Electrode* (FC1, FC2, Cz). ANOVA showed significant differences in *Condition* ($F[1, 29] = 34.26$, $p < 0.001$, $\eta_p^2 = 0.54$), due to higher positivity in the invalid condition with respect to the valid condition; *Electrode* ($F[1.67, 48.44] = 18.52$, $p < 0.001$, $\eta_p^2 = 0.39$); *Condition* × *Electrode* ($F[1.77, 51.33] = 4.44$, $p < 0.020$, $\eta_p^2 = 0.13$); and *Condition* × *Block* × *Electrode* ($F[2.5, 72.68] = 3.41$, $p < 0.029$, $\eta_p^2 = 0.10$).

A three-factors repeated measures ANOVA was performed on the voltage data of the P3b time window (380–530 ms after the auditory target). Factors were: *Condition* (valid, invalid), *Block* (50%, 68%, 86%) and *Electrode* (P3, Pz, P4, POz, O1, Oz, O2). ANOVA showed significant differences in *Condition* ($F[1, 29] = 75.66$, $p < 0.001$, $\eta_p^2 = 0.72$), due to an increased voltage in the invalid condition with respect to the valid condition; *Electrode* ($F[2.72, 78.90] = 4.74$, $p < 0.006$, $\eta_p^2 = 0.14$); *Condition* × *Block* ($F[1.96, 56.99] = 12.39$, $p < 0.001$, $\eta_p^2 = 0.29$); and *Condition* × *Electrode* ($F[3.14, 91.06] = 8.52$, $p < 0.001$, $\eta_p^2 = 0.22$). The Bonferroni comparisons were applied to the interaction *Condition* × *Block* showing significant differences: 86%>50% (p<0.003). Also, if no multiple comparisons are taken into account, there were significant differences in the other two contrasts: 86%>68% (p<0.022) and 86%>50% ($p < 0.020$).

These results show that the P3a component was higher in the invalid condition compared to the valid condition, but the *Condition* × *Block* interaction was not significant (Fig. 6D). Instead, the P3b component was higher in the invalid condition, compared to the valid condition, as the proportion of valid trials per block increased (Fig. 6E).

2.2.6. Negative slow wave component

The NSW was located in fronto-central areas (Figs. 4 and 5). A three-factors repeated measures ANOVA was performed on the voltage data of the time window (380–530 ms after the auditory target). Factors were: *Condition* (valid, invalid), *Block* (50%, 68%, 86%) and *Electrode* (FP1, FPz, FP2, F3, Fz, F4). ANOVA showed significant differences in *Condition* ($F[1, 29] = 31.19$, $p < 0.001$, $\eta_p^2 = 0.51$); and *Condition* × *Block* ($F[1.99, 57.76] = 8.41$, $p < 0.001$, $\eta_p^2 = 0.22$). The Bonferroni comparisons were applied to the interaction *Condition* × *Block* showing one significant difference: 86% > 50% ($p < 0.003$). Also, if no multiple comparisons are taken into account, there was another significant difference: 68% > 50% ($p < 0.020$). These results indicate that there was a higher difference −valid vs. invalid- on the NSW, as the proportion of valid trials per block increases (Fig. 6F).

2.2.7. Regression of lateralized CNV and P3b invalidity modulation

As indicated in the methods section, the subtraction of the lateralized CNV and P3b invalidity modulation in 86% and 50% blocks was regressed (Fig. 7A). This regression showed a clear outlier. In order to decide if to eliminate or not this subject from the regression, the standardized residuals of the lateralized CNV vs. P3b modulation were obtained and, as the regression residuals of this subject was >3SD (Fig. 7B), it was eliminated for a subsequent regression analysis. As a result, Fig. 7C shows a positive correlation between the lateralized CNV and the P3b invalidity modulation, indicating high P3b modulation in subjects that presented high lateralized CNV amplitude.

3. Discussion

The present study is designed to analyze the cognitive-related dynamic modulation, as indexed by ERPs, which allows subjects to adapt their behavior to the continuous changes that occur in the environment. CCPP makes it possible to observe the neural

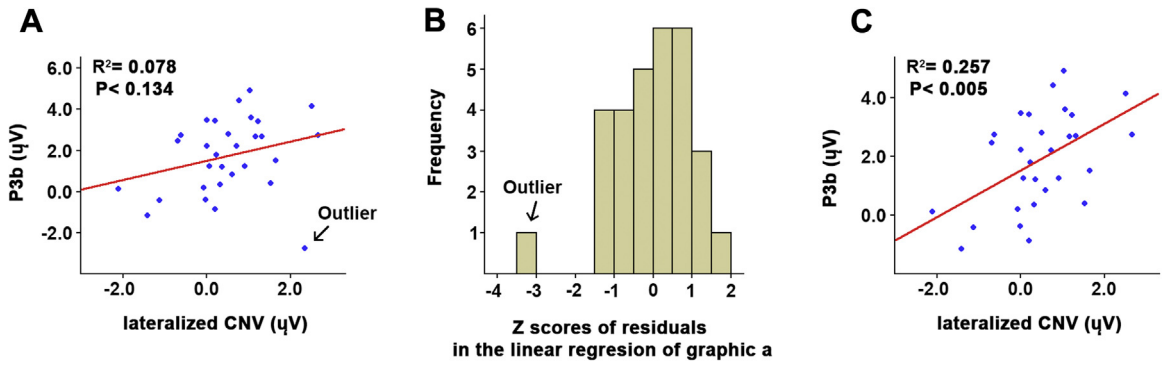

Fig. 7. Relationship between the lateralized CNV and P3b modulation by invalid targets. Fig. 7A shows the regression of the lateralized CNV amplitude and the P3b invalidity modulation in the subtraction of 86% minus 50% validity block. Fig. 7B shows the standardized residuals of the lateralized CNV amplitude vs. P3b modulation. Notice that the regression residuals of the outlier was >3SD. Fig. 7C shows the positive correlation between the lateralized CNV amplitude and the P3b invalidity modulation (excluding the outlier), indicating high P3b modulation in subjects that presented high lateralized CNV amplitude.

processing of the cue-target stimuli in two different experimental conditions: Valid and Invalid. This adaptive processing was analyzed through the influence of the so-called 'spatial cueing effect' on RTs, Anticipations, Incorrect responses and the ERPs that occurred after the arrival of the cue (CNV) and the target (N1, P2a, P2p, P3a, P3b and NSW). Previous results suggest that the modulation of behavior and ERPs reflects the dynamic change in the credibility assigned to the cue as a function of previous trial conditions (Arjona & Gómez, 2011; Gómez & Flores, 2011; Jongen & Smulders, 2007).

First, the results show an effect of trial condition (valid and invalid) on behavioral (RTs and Incorrect responses) and neural (P2p, P3a and P3b and NSW components) responses, indicating that the neural system is clearly detecting the accuracy and/or inaccuracy of the predicted target position. This effect is similar to the one obtained in previous studies (Arjona et al., 2014; Arjona & Gómez, 2011, 2013; Jongen & Smulders, 2007). On the other hand, by changing the proportion of validity/invalidity through the different trial blocks (50%, 68% and 86% of valid trials), a significant *Condition* × *Block* interaction was obtained on the RTs, due to a pattern generated by the spatial cueing effect: 86% > 68% > 50%. In the same vein, the Incorrect responses and the lateralized component of CNV, P2a, P3b and NSW also showed a significant *Condition* × *Block* interaction.

3.1. Behavioral results

Previous studies have shown that the ratio of validity/invalidity in the cue-target combination influences attentional allocation, with high valid cues increasing the magnitude of the validity effect (Jonides, 1983; Riggio & Kirsner, 1997; Vossel et al., 2013). The present behavioral analysis showed that the spatial cueing effect on RTs (difference between valid and invalid trials) was higher as the proportion of valid trials per block increased. An explanation for this behavioral pattern would be related to an increase in the sensory-motor preparation generated by the cue as the percentage of valid trials per block increases. A higher proportion of previous valid trials would increase the credibility of the cue on the next valid trials. Consequently, the sensory and motor attentional resources would be strongly oriented toward the cue direction, improving target perception and hand-response execution. By contrast, a higher proportion of previous invalid trials would diminish the credibility of the cue on the next valid trials, reducing the attentional orientation to the target location and increasing the RTs. Based on a Bayesian framework, the *a priori* conditional probability of a valid 'cue-target' combination in a given trial would increase as the proportion of valid trials per block increases. The process would consist of modifying the *a priori* conditional probabilities (p (S2/S1)) as a function of previous trial outcomes (Feldman & Friston, 2010; Gómez & Flores, 2011). Furthermore, the percentage of Incorrect responses in invalid trials, compared to valid trials, was higher as the proportion of valid trials per block increased. This result would be interpreted as higher impulsive responses to the invalidly cued position as the credibility of the cue increases. Subjects would prepare more to respond to the cued location on invalid trials preceded by a higher proportion of valid trials (blocks with 86% valid trials).

3.2. Event related potentials

The ERPs obtained in the present experiment would help to understand how the validity probability (proportion of valid trials per block) modulates the different cognitive operations related to processing the validity/invalidity effect in CCPP.

3.2.1. Cognitive negative variation (CNV)

The CNV was analyzed in the present study through the comparison of blocks of trials with different proportions of valid/invalid trials. From this broader perspective, the central electrodes of CNV did not show an influence generated by the type of block (Supplementary Fig. S1 in the online version at DOI: 10.1016/j.biopsycho.2016.07.001). The lack of differences in the amplitude of central CNV would possibly be due to the short cue-target period (360 ms) that would have limited the time for building up a CNV expressing the predictability of the cue. In this sense, Scheibe, Schubert, Sommer, and Heekeren (2009), in a previous experiment in which the prior probability of targets was also controlled (but the S1–S2 period was 2 s), showed that the CNV amplitude changed accordingly.

The lateralized component of CNV (Fig. 3) showed significant differences in the comparison between blocks (86% > 50%). This result indicates that a higher proportion of valid trials per block generates an increased preparation to respond, contra-lateral to the side indicated by the cue. It is possible that this preparation includes, not only motor, but also sensory aspects. In this sense, in a similar CCPP that in present report, but using Magnetoencephalography (MEG), Gómez et al. (2004), showed that during the CNV period, not only the motor cortex, but also the auditory cortex contralateral to the indicated location, was activated. The presentation of the cue would be enough to trigger a warning, although a limited transfer of activation to sensory-motor areas would occur in the block of 50% validity/invalidity.

The increase of amplitude in the lateralized CNV would represent the macroscopic correlate of an increase in baseline neural activity. Baseline shifts have been proposed as a mechanism for neural implementation of prior probabilities (Summerfield & de

Lange, 2014), and the lateralized CNV would index such excitability changes due to continuous influx of positive charge in the apical dendrite of pyramidal neurons (Rockstroh et al., 1982), possibly representing the neural implementation of priors. The present results incorporate the notion of 'expectation' to refer to a dynamic process which is created as a function of trials outcome (Arjona et al., 2014; Chennu et al., 2013). The increase of the block cue-validity is transferred to the CNV as an increase of the cue-induced lateralized CNV.

3.2.2. N1 and P2a components

In present report, N1 results showed a significant interaction *Condition* × *Block*, but Bonferroni analyses did not show significant differences between blocks. The most likely cause of this lack of N1 auditory modulation must be the opposite effect of attentional and predictive processes (Summerfield & de Lange, 2014). In a similar experiment to that of present report, but with only one type of block (80% of validity), an increase in the N1 amplitude, for validly cued targets with respect to invalidly cued targets, was obtained (Arjona & Gómez, 2013). A reassessment of our previous results indicates that the effects of N1 were too occipital to be considered a modulation of N1, but rather an increased positivity of the early face of the P2p component in invalidly cued targets which would decrease the surface N1 amplitude in this condition. In this sense, the analysis of N1 amplitude induced by the second target of the sequences valid–valid and invalid-valid, showed an increased N1 amplitude in the invalid–valid with respect to the valid–valid sequences. These results might be interpreted as an increase of N1 amplitude in attended validly cued trials, in which prediction of the cue is reduced by the previous invalid trial. This idea would be compatible with the proposal of two opponent processes for the N1 component (Lange, 2013). Moreover, Todorovic, van Ede, Maris, and de Lange (2011) and Todorovic and de Lange (2012), in a two tones task (similar to that used to obtain the P50 component), found that predictability reduced the amplitude of middle latency Event Related Fields in a latency compatible with the auditory N1 component. Therefore, the different trends between the attentional effects (increase of N1 in validly cued targets) and the target prediction effects (decrease of N1 in validly cued targets), would result in the obtained absence of significant effects for N1 in present task.

On the other hand, the increased amplitude of the P2a component in validly cued targets suggests that P2a is related to increased attention in valid trials. P2a would be an auditory prefrontal positivity related to frontal regulatory mechanisms of selective attention (Potts, Dien, Hartry-Speiser, McDougal, & Tucker, 1998). In present study, the auditory P2a was higher in the valid condition (attended stimulus), compared to the invalid condition, and the effects were bigger in the blocks of 86% and 68% compared to 50%. In previous experiments, this component has shown the same medial frontal spatial distribution as response to different targets, including auditory and visual stimulus, and with different response tasks, suggesting that it is more related to the relevance of the stimuli (attended/unattended or valid/invalid) than to the characteristics of the perception process or the response modality required in the current task (Potts et al., 1998; Potts, 2004; Potts, Patel, & Azzam, 2004; Potts & Tucker, 2001). In this sense, auditory P2a would be similar to the visual Frontal Selection Positivity (FSP) (Kenemans, Kok, & Smulders, 1993; Makeig et al., 1999; Potts, 2004), which has been related to the process of task-relevant stimuli in the transition from the selection of relevant features to the selection of responses (Makeig et al., 1999). Following this lead, the P2a may be interpreted as an attention-modulated process required for performing an auditory discrimination task related to a response. Thus, present result would be reflecting an attentional process which grows after perception of valid targets, in comparison to invalid targets, as the proportion of valid trials per block increased.

3.2.3. P2p, P3a and P3b components

Previous studies associate the visual modality of the P2p component with processes related to memory systems (Freunberger, Klimesch, Doppelmayr, & Holler, 2007; Taylor, Smith, & Iron, 1990; Wolach & Pratt, 2001). The present study shows an auditory modality of the P2p (Figs. 4 and 5), previously observed in an experiment that used a similar paradigm (Arjona & Gómez, 2013). The results presented here indicate a higher P2p positivity in invalid trials compared to valid trials, although there were no significant amplitude differences between the blocks. It is difficult to propose a specific function for this increased P2p in invalidly cued targets, but two possible hypotheses can be suggested. On the one hand, the first possibility arises from the inversion of polarity in the P2 latency in anterior (P2a) with respect to posterior (P2p) sites when invalid trials are subtracted from valid trials. Such a topography would suggest midline increased activity in invalid trials, indicating that the difference wave at the latency of P2 would be reflecting the activation of medial areas related to the conflict analysis (Botvinick et al., 2004), with the conflict being higher in invalid trials than in valid trials. On the other hand, the P2p component would be related to the encoding of the target information by the working memory as an earlier stage of the posterior P3b. Therefore, the unexpected arrival of the target on the opposite side to the one indicated by the cue may generate a higher updating of working memory to encode the new information. This process would represent an initial phase in the change of conditional probabilities (p (S2/S1)). The hierarchical structure of the Bayesian brain model (Friston, 2009) suggests that lower order cortices receive priors from higher order cortices and would update their own model based on its prediction error. These early differences in P2p between valid and invalid trials would be indexing the lower order cortex prediction error and updating. Nonetheless, any claim about the functional meaning of the P2p should remain at a merely speculative level.

Regarding the P3a and P3b components, previous research reported that these components have their maximum potential in invalid trials compared to valid trials, in both the visual and the auditory modality (Arjona & Gómez, 2013; Digiacomo, Marco-Pallarés, Flores, & Gómez, 2008 Golob et al., 2002; Gómez et al., 2008; Mangun & Hillyard, 1991). Although in the present study P3a and P3b presented higher amplitude in invalid trials, compared to valid trials, only P3b shows a higher difference between conditions as the proportion of valid trials per block increases.

P3a is generated as a brain response to novel stimuli (compared to more frequent stimulation), which requires a shift of attention (Dien, Spencer, & Donchin, 2003; Escera, Alho, Winkler, & Näätänen, 1998; Friedman, Cycowicz, & Gaeta, 2001; Polich, 2007). In CCPP, the enhancement of P3a in invalid trials would be related to an attentional reorientation elicited by the unpredicted target (Gómez et al., 2008). Also, it has been observed that both, the frequency of the presentation of the stimulus and the subjective expectancy of the target, are related to the generation of the P3a component in visual (Digiacomo et al., 2008; Gómez et al., 2008) and auditory modality (Arjona & Gómez, 2013). Therefore, it can be proposed that P3a in CCPP represents the activation of brain networks related to the supramodal surprise associated with the presentation of unexpected target locations. In the current study, although the *Condition* × *Block* interaction was not significant, there was a higher P3a in the invalid condition compared to the valid condition (Figs. 4–6D). This result probably reflects the need for attentional reorientation in the three blocks, even the 50% block, which includes the implicit directional value of the cue.

P3b corresponds to a late positive component elicited around 400 ms after the presentation of an infrequent stimulus

Table 1
Summary of the significant *Condition effects* and interactions *Condition* × *Block* (Behavior and ERPs).

	Condition effect	*Condition* × *Block (Bonferroni comparisons)*
Reaction Times (ms)	Valid < Invalid	86% > 68% (p<0.003) 86%>50% (p<0.003) 68%>50% (p < 0.003)
% Anticipations	Valid > Invalid (68%)	–
% Incorrect Responses	Valid < Invalid	86% > 68% (p<0.012) 86%>50% (p < 0.006)
N1	–	–
P2a	–	86% > 50% (p<0.036) (V>I) 68% > 50% (p<0.030) (V>I)
P2p	Valid < Invalid	–
P3a	Valid < Invalid	–
P3b	Valid < Invalid	86% > 50% (p < 0.003)
Slow Wave	Valid < Invalid	86% > 50% (p < 0.003)
	Condition effect	*Block effect*
CNV (central)	Not apply	–
CNV (lateralized)	Not apply	86% > 50% (p < 0.048)

(Duncan-Johnson & Donchin, 1977, 1982; Squires, Wickens, Squires, & Donchin, 1976). Previous reports (Arjona & Gómez, 2013; Gómez & Flores, 2011) have proposed that the P3b modulation in CCPP during invalid trials would also be related to the updating of the *a priori* values of (S2/S1). In this line, the present results reflect a higher P3b generated by invalidly cued targets, compared to validly cued targets, as the proportion of valid trials per block increases (Figs. 4–6E). This effect suggests an "updating" of the cue-target conditional probability representation in invalid trials, which is higher as the proportion of valid trials per block increases. In sum, the growth pattern of the P3b component in invalid trials is, perhaps, reflecting the so-called process of 'working memory updating' (Donchin & Coles, 1988) of the subjective probability generated on every trial (Sommer, Leuthold, & Matt, 1998; Arjona & Gómez, 2013).

In the context of the Bayesian brain hypothesis (Friston, 2009), the increase of P3b in invalid trials would be related to the processes of prediction error generation and/or the updating of the conditional probabilities (p (S2/S1)) (Gómez & Flores, 2011). In this line, the positive correlation between lateralized CNV and P3b modulation by invalid targets, supports the bayesian nature of P3b operation. CNV is related to the selection of a neural set and its activity intensity (Arjona et al., 2014; Chennu et al., 2013; Gómez et al., 2001), and the activation of this neural set is needed for the processing of the targets (Gómez et al., 2001), with the current value of the conditional cue probability (p(S2/S1)). Therefore, if the modulation of P3b is related to the p(S2/S1) updating, some sort of quantitative relationship must exist between the amplitude of CNV and the modulation of P3b in invalid trials. In fact, this is the result obtained in the regression analysis (Fig. 7C).

3.2.4. Negative slow wave component

The modulation of the NSW by invalid trials showed an increase in amplitude as the proportion of valid trials per block increased (Fig. 4). This component appears in frontal areas at a similar latency to P3b, and some authors (Van Leeuwen et al., 1998; Flores et al., 2009) have argued that, particularly in children, it would correspond to the negative side of posterior positive dipoles. However, in the auditory modality, a genuine frontal origin for the NSW has been demonstrated by a dissociation between the effects of the dorsolateral prefrontal cortex lesion on P3b and the NSW (Lovstad et al., 2012). From a functional point of view, the frontal negativity around the P3b latency has been described, in the auditory modality, as a response to distractors, and it has been suggested that represents the reorientation effort after distracters or the so-called reorientation negativity (Wetzel & Schröger, 2014). In this sense, the increase of frontal negativity in low probability invalid trials would correspond to the effort to focus attention in the cue after a non-expected target. An alternative view indicates a relationship of the NSW with the orienting and alerting response (Rohrbaugh, Syndulko, & Lindsley, 1979), more clearly visualized in the orienting early CNV response to the alerting S1 stimulus (Walter et al., 1964). If previous interpretation is assumed, an increased level of alerting would occur after non-expected targets as the proportion of valid trials per block increases. In any of the two previous interpretations, one possibility is that low probability invalid trials would demand an increased late processing of cue validity in order to influence the neural preparation induced by the cue in next trial, which is a phenomenon demonstrated when sequential analyses are performed in CCPP (Gómez and Flores, 2011).

3.3. Conclusions

The present report shows a broader approach to the analysis of the behavioral and ERP effects generated by the valid and invalid cueing of auditory targets: **(i)** the influence of the spatial cueing effect on behavior (RTs and incorrect responses) is higher as the proportion of valid trials per block increases; **(ii)** the lateralized component of CNV indicate higher sensory-motor preparation to respond as the proportion of valid trials per block increases; **(iii)** P2a shows higher attentional modulation generated by the perception of expected targets, compared the perception of unexpected targets, as the proportion of valid trials per block increases; **(iv)** P2p and P3a represent higher working memory updating and attentional reorientation, respectively, after perception of unexpected targets; **(v)** the P3b component shows higher updating of the cue credibility in invalid trials, compared to valid trials, as the proportion of valid trials per block increases; and **(vi)** the higher NSW after low probability invalid targets indicates the demand for attentional reorientation and/or the post-target alerting, in order to influence next trial processing.

Overall, although a neat block pattern for the spatial cueing effect was only obtained for RTs (86% > 68% > 50%), a considerable number of ERP effects were obtained in relation to the validity blocks (Table 1). Thus, the present results suggest a more intense spatial cueing effect as the proportion of valid trials per block increases.

4. Materials and methods

4.1. Participants

Thirty subjects (15 female and 15 male) between 18 and 35 years of age (mean: 24 years old and SD: 4.22) who participated in the experiment were fully analyzed. The experiments were conducted with the informed and written consent of each subject, following the rules of the Helsinki Convention. The Ethics Committee of the University of Seville approved the study.

4.2. Stimuli and behavioral paradigm

The stimulus presentation and response recordings were computer-controlled (E-Prime 2.0). Participants were seated at 60 cm from a computer screen. The subjects participated in a modified version of the CCPP, in which the central cues were arrows appearing at the center of the screen, followed by monaural auditory stimulation (Fig. 1). The central arrow stimulus (S1) was considered the spatial orientation cue, and the monaural auditory stimulus (S2) was the imperative one (1000 Hz and 89 db). The auditory stimuli were delivered to the subject's ears through headphones. Participants were instructed to fixate their eyes on a white cross in the center of the screen and pay attention to the stimulus sequence in every trial (S1–S2). They were informed that the central arrow (S1) acted as a cue that indicated the possible location where the sound would appear, but not always the correct location. After the arrow presentation, subjects had to press the right button as quickly as possible with the index finger of the right hand if the S2 appeared in the right ear or the left button with the left index finger if the S2 appeared in the left ear. The response device was the Cedrus (model RB-530). The events sequence within a trial was as follows: (i) a central fixation white cross appears for 300 ms;(ii) the S1 is on for 300 ms; (iii) an expectancy period (with the white cross) lasts for 370 ms (therefore, the total S1–S2 period was 670 ms); (iv) the S2 comes on for 100 ms and is randomly presented to the left or right ear with equal probability (0.5); and (v) the response time is on for 1000 ms (with the white cross again) (Fig. 1).

The experiment consisted of 600 trials divided into 6 blocks (100 trials per block), and there were three types of blocks:

>50% → in 50% of the trials the S1 points to the correct location where the S2 will appear (valid trials) and in the other 50% the S1 points to the wrong location (invalid trials).

>68% → in 68% of the trials the S1 points to the correct location, and in the other 32% it points to the wrong location.

>86% → in 86% of the trials the S1 points to the correct location and in the other 14% it points to the wrong location.

The 30 participants were divided into six groups. Each group performed a different order of presentation of the blocks (6 block orders). In this way, the different orders of block presentation are counterbalanced, and the possible effect caused by the influence of the previous type of block was canceled. There were twelve training trials.

4.3. EEG recording, processing and analysis

The EEG was recorded from 32 scalp sites in an extended version of the International 10–20 System, using tin electrodes mounted on an electrode cap (Electrocap). Eye movements (EOG) were recorded from two electrodes at the outer canthus of each eye for horizontal movements, and from one electrode under the left eye for vertical movements, referenced to one electrode above the left eye. Impedance was maintained below 5 KOhms. Data were recorded in DC using a common average as reference, and they were not filtered. The ground electrode was located on the line between Fpz and Fz. The amplification gain was 20.000, and the data were acquired at a sampling rate of 512 Hz (ASA-lab EEG/ERP system, ANT, Holland).

EEG recordings were analyzed with the EEGlab v10.0.0.0b (Delorme & Makeig, 2004) and Matlab R2010a (MathWorks Inc., MA, USA) software packages. To eliminate AC power line interference and blink artifacts in the EEG, an Independent Components Analysis (Groppe, Makeig, & Kutas, 2008) was performed. Criteria for determining these artifactual components were their scalp map distribution, time course and spectral power. For instance, the eye blink artifact component showed a frontal location, coincided with blinking in the recording of eye movements, and showed low frequency in the power spectrum. These components were discarded, and the EEG signal was reconstructed.

An offline filtering of 0–30 microvolts was used on the ERPs. Two baselines were used to compute the ERPs; (i) for the CNV was the −200 to 0 ms interval before the cue stimuli; and (ii) for N1, P2a, P2p, P3a and P3b was the −200 to 0 ms interval before the target stimuli. All the epochs for which the EEG exceeded ±90 microvolts in any channel were automatically discarded from ERP analysis. Artifact corrected recordings were averaged off-line using a rejection protocol based on the voltage amplitude. The algebraically-linked mastoids were computed off-line and used as a reference for analytical purposes. ERPs were obtained for each subject by averaging the EEG, using the switching-on of the cue as a trigger.

4.4. Analysis of reaction times, errors and event related potentials

RTs, Anticipations (responses faster than 180 ms after the onset of the auditory target), Incorrect responses (responses on the side opposite to the stimulated ear) and Omissions (no responses) were computed and statistically analyzed.

After visual ERPs, the CNV (central and lateralized electrodes) induced by the central arrow and six components generated after the auditory target (N1, P2a, P2p, Negative Slow Wave, P3a and P3b) were analyzed.

The lateralized component of CNV was performed with the same method as the so-called Lateralized Readiness Potential (LRP) (Eimer, 1993), but is not elicited by the same type of experimental paradigms that the one used for the LRP (self-paced movements). The formula is computed as the mean voltage difference between hemispheres when the central arrow pointed to the left and to the right. For instance, to compute the F3-F4 electrodes, the following formula was applied:

$$((F3\text{-}F4)Leftarrow - (F3\text{-}F4)Rightarrow)/2$$

Statistical analyses of the type of Errors were computed by the Wilcoxon Signed-Ranks test because they were not normally distributed variables (Shapiro-Wilk test of normality). Instead the RTs and ERPs were performed using repeated-measures ANOVA. The *P* values were estimated by the Greenhouse-Geisser correction and the partial eta-squared values were calculated as a measure of the effect size (SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc.). The mean voltages in selected time windows were analyzed independently for the different components. The electrode group for each component was selected based on the topography results obtained in a previous experiment using the same CCPP (Arjona & Gómez, 2013).

The factors *Condition* (valid, invalid) and *Block* (50%, 68%, 86% of validity proportion) were used for the statistical analysis of behavior and ERP data (*Electrode* was an additional factor in ERPs). The main objective was to demonstrate that the spatial cueing effect is different between the three blocks.

T-tests, with Bonferroni corrections for multiple comparisons, were computed in the cases of significant *Condition* × *Block*

interaction (differences in the spatial cueing effects between blocks). These Bonferroni comparisons were restricted to the previously indicated interaction, due to the primary interest of the present report (analyze how the validity/invalidity effect was affected by the proportion of validity in the different blocks).

Finally, in order to observe the possible relationship between the amplitude of the lateralized CNV and the modulation of the P3b by invalidity, a linear regression was computed between the most extreme proportion of validity blocks; (i) Lateralized CNV in the 86% validity block minus lateralized CNV in the 50% validity block; and (ii) P3b invalidity modulation in the 86% validity block minus P3b invalidity modulation in the 50% validity block.

Acknowledgement

This work has been possible thanks to grants from Ministry of Science and competitiveness (FEDER FUNDS) PSI2013-47506-R and from the Consejería de Innovación, Ciencia y Empresa of the Junta de Andalucía.

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Neuroscience Research 115 (2017) 37–43

Contents lists available at ScienceDirect

Neuroscience Research

journal homepage: www.elsevier.com/locate/neures

Event related potentials changes associated with the processing of auditory valid and invalid targets as a function of previous trial validity in a Posner's paradigm

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ARTICLE INFO

Article history:
Received 12 July 2016
Received in revised form 7 September 2016
Accepted 16 September 2016
Available online 3 October 2016

Keywords:
Sequential effects
Priors updating
Attention
Working memory
Beyesian inference

ABSTRACT

The present study tries to analyze the neural basis of the so-called "Inter-trial Validity–Invalidity Effects" by means of Event-Related Potentials. The N1, P2, P3a and P3b components were examined. The aim is to show the sequential effects on Event-Related Potentials by analyzing the effect of previous trial condition (n – 1) in the processing of current trial target (n). Event-Related Potentials results indicate that the N1 and P2 components show higher negativity in valid trials preceded by invalid trials with respect to valid trials preceded by valid trials, elicited by the so-called "Processing Negativity". Next, the P3a and P3b components show increased positivity in invalid trials preceded by valid trials compared to invalid trials preceded by invalid trials. Present results suggest that there is a dynamic updating of attentional resources and working memory, due to the influence of previous trial condition (n – 1) on the current trial processing (n). This dynamic updating would be higher after trial validity changes, and it would be compatible with the Bayesian Brain Model.

1. Introduction

In Central Cue Posner's Paradigm (CCPP) (Posner, 1980), the central cue (S1) may validly or invalidly indicate the spatial location of the upcoming target (S2). Based on this, faster and more accurate responses have been found when the cue direction matches the target location (valid trials) than when they are discordant (invalid trials) (Arjona and Gómez, 2013). This effect has been called the "Validity Effect", and it refers to the cost produced by rearranging attentional resources from the opposite side to the one indicated by the cue (Posner, 1980; Posner et al., 1982; Jonides, 1983; Riggio and Kirsner, 1997). The so-called "Inter-trial Validity–Invalidity Effect" (Arjona and Gómez, 2011, 2013; Jongen and Smulders, 2007; Gómez et al., 2009; Arjona et al., 2014) would also appear in CCPP. This effect reflects the influence that the assessment of the validity/invalidity in one particular trial (n – 1) has on the next trial performance (n).

Different auditory studies have shown that attended stimuli elicit an enhanced N1 component, compared to unattended stimuli (Arjona and Gómez, 2013; Parasuraman, 1980; Hillyard et al., 1973; Woldorff and Hillyard, 1991; Woldorff et al., 1993; Fabiani et al., 2000). There is also a fronto-central negative shift, the so-called "Processing Negativity" (PN) (Näätänen et al., 1978; Näätänen and Michie, 1979; Hansen and Hillyard, 1980; Alho et al., 1987), which increases as a result of processing attended stimuli. Some studies mention the influence of the PN, not only in N1, but also in the P2 component (Näätänen and Michie, 1979; Michie et al., 1990).

On the other hand, invalid trials trigger an increase in P3a and P3b components, reflecting the assessment of the incorrect cue information and the updating of the cue-target conditional probability (Gómez and Flores, 2011; Mangun and Hillyard, 1991; Eimer, 1993; Gómez et al., 2008). The increase of P3b amplitude in invalid trials with respect to valid trials would be a function of the cue validity probability, suggesting that P3b indexes the difference between the spatial prediction induced by the cue and the current location of the target (Arjona and Gómez, 2016). The fact that these components are related to beliefs updating and predictive surprise has also been proposed in experiments in which the subjects have to

Abreviations: CCPP, Central Cue Posner's Paradigm; PN, Processing Negativity; EOG, electrooculography; EMG, electromyography; ERPs, Event-Related Potentials; RTs, Reaction Times; VV, valid–valid; IV, invalid–valid; II, invalid–invalid; VI, valid–invalid.

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http://dx.doi.org/10.1016/j.neures.2016.09.006
0168-0102/

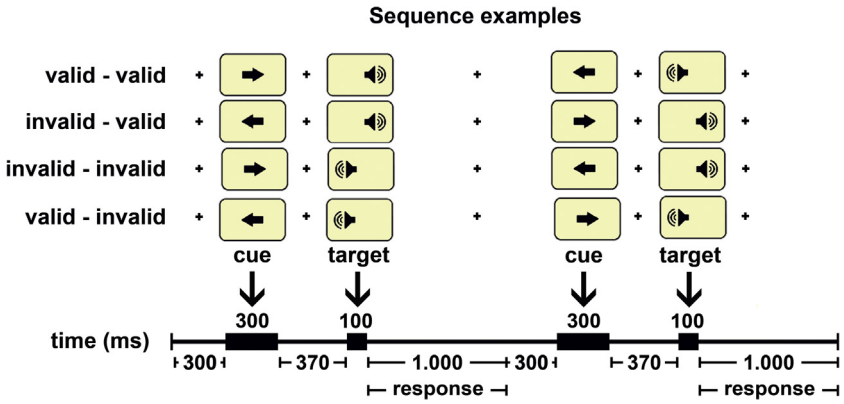

Fig. 1. Experimental paradigm.
Representation of the one-trial and two-trial structure for the different types of dyads in the experiment. The temporal sequence of stimulus presentation appears in the lower part of the figure. The central arrow (cue) was presented in the center of the screen, and the auditory stimulus (target) was presented monaurally.

infer the type of urn from which balls are extracted (Kolossa et al., 2015; Seer et al., 2016). One last interpretation is related to the predictive coding hypothesis (Friston, 2009) and, in the context of present experiment, implies that subjects would generate *a priori* conditional probabilities for the different cues (S1) as predictors of upcoming events (S2). They would also change these conditional probabilities (p (S2/S1)) based on the outcome of current trial, and so the behavior would continually adapt to the environment (Friston, 2009; Bruce and Tsotsos, 2009; Reynolds and Heeger, 2009; Feldman and Friston, 2010; Gómez and Flores, 2011). It is important to mention that the model proposed by Friston (2009), known as the 'Bayesian Brain Model', proposes that the brain operates based on a similar dynamic to Bayesian Statistics. In this context, the concept of 'Prediction Error' arises as the signal that causes the change in these probabilities, which would correspond, at the neural level, to changes in synaptic weights (Friston, 2009; Kopp, 2008; Gómez et al., 2008; Feldman and Friston, 2010; Gómez and Flores, 2011).

Based on previous results, four hypotheses can be proposed for the auditory target processing in the second trial of a two trials sequence. These four hypotheses are: (i) a higher PN will be obtained in the IV sequence, compared to the VV sequence, given that, in both sequences, the second target is attended to, but the IV sequence needs extra attentional effort (due to the lower credibility of the cue after an invalid trial) in the processes of orientation and perception of the auditory target; (ii) an increased PN will emerge in the VI sequence, compared to the II sequence, due to the greater effort needed to process the invalidly cued target after a valid trial because the attention deployed on the wrong side (indicated by the cue) will be higher in the invalid trial preceded by a valid trial than in the invalid trial preceded by another invalid trial; (iii) an increase in the P3a and P3b amplitude will be observed in the IV sequence, compared to the VV sequence, due to the higher processing of the unexpected valid target after an invalid one; (iv) an increase in the P3a and P3b amplitude will be observed in the VI sequence, compared to the II sequence, due to the higher processing of the unexpected invalid target after a valid one.

The present report complements previously published reports. Each of our previous publications corresponds to different insights (behavioral and neural responses (Jongen and Smulders, 2007)) of the sequential effects in the CCPP: (i) behavioral effects (Reaction Times, Anticipations, Incorrect responses, and Total errors) in the last trial of two-trial and three-trial sequences (Arjona and Gómez, 2011); (ii) ERPs (Contingent Negative Variation (CNV), N1, P2, P3a and P3b) in valid and invalid trials (Arjona and Gómez, 2013); (iii) Pre-target ERPs (Early Directing Attention Negativity (EDAN), CNV and Lateralized Readiness Potential (LRP)) in the second trial of two-trial sequences (Arjona and Gómez, 2013; Arjona et al., 2014). The present paper concludes the study by analyzing the post-target ERPs (N1, P2, P3a and P3b) in the second trial of two-trial sequences. Therefore, the novelty would be to understand how the processing of a target is modulated by the outcome of the previous trial.

2. Material and methods

2.1. Subjects

Thirty-four subjects participated in the experiment, but only 29 subjects (16 females; 13 males) between 19 and 35 years of age (mean: 24 years old; SD: 2.87) were fully analyzed. Five subjects with a high number of EMGs, eye movements, blink artifacts and trend derived contaminations in the EEG were excluded from the analysis. The experiments were conducted with the informed and written consent of each subject, following the rules of the Helsinki Convention. The Ethics Committee of the University of Seville approved the study.

2.2. Stimuli and behavioral paradigm

Participants were seated 60 cm from a computer screen. The subjects participated in a modified version of the CCPP, in which the central cues were arrows appearing in the center of the screen, followed by monoaural auditory stimulation (Fig. 1). The central arrow stimulus was considered the spatial orientation cue (S1), and the monoaural auditory stimulus was the imperative one (S2). The auditory stimuli were delivered to the subject's ears through headphones. Participants were instructed to fixate their eyes on a white cross in the center of the screen and pay attention to the ear indicated by the central arrow. They then had to press the right button as quickly as possible if the auditory stimulus appeared in the right ear, or press the left button if the auditory stimulus appeared in the left ear (with the index finger of the compatible hand). The response device was the Cedrus model RB-530. The auditory stimulus (1000 Hz) was randomly presented to the left or right ear with equal probability (.5). The stimulus had an intensity of 89 dB.

Each subject was presented with a total of 500 trials divided into five blocks. The central arrow (S1) had directional information: in half of the trials it pointed to the right, and in the other half to the left. In 80% of the trials the central arrow gave correct information about the target location (V: valid trials), and in 20% of the trials the central arrow pointed to the ear opposite to where the auditory stimulus would appear (I: invalid trials). Subjects were

informed that the visual cue had informative value, indicating with high probability the location of the auditory stimulus.

2.3. EEG recording and analysis

The stimulus presentation and response recording were computer-controlled (E-Prime 2.0). The EEG was recorded from 64 scalp sites in an extended version of the International 10–20 System, using tin electrodes mounted in an electrode cap (Electro-cap, inc). Eye movements (EOG) were recorded from two electrodes at the outer canthus of each eye for horizontal movements, and from one electrode under the left eye for vertical movements, referenced to one electrode above the left eye. Impedance was maintained below 5 kΩ. Data were recorded in DC using a common average as reference, and they were not filtered. Only for presentation in figures, the Event-Related Potentials (ERPs) were low-pass filtered (15 Hz). Ground electrode was localized in the line between Fpz and Fz. The amplification gain was 20.000 (ASA-lab EEG/ERP system, ANT, Holland). The data were acquired at a sampling rate of 256 Hz, using a commercial AD acquisition and analysis board (Eemagine EEG, ANT, Holland).

EEG recordings were analyzed with the EEGlab v10.0.0.0b and Matlab R2010a (MathWorks Inc., MA, USA) software packages. To eliminate AC power line interference and blink artifacts in the EEG, an Independent Components Analysis was performed. Criteria for determining these artifactual components were their scalp map distribution, time course and spectral power. The eye blink artifact component showed a frontal location, coincided with blinking in the recording of eye movements, and showed low frequency in the power spectrum. Instead, electromyography (EMG) artifact component presented a high frequency and a temporal topography. These components were discarded, and the EEG signal was reconstructed. The segmented epochs had a duration of 2200 ms. The baseline was the 200–0 ms interval before the cue stimuli. The algebraically-linked mastoids were computed off-line and used as a reference for analytical purposes.

The amplitude of the N1, P2, P3a and P3b (early and late) components was analyzed in the second trial of two trials sequences. Two repeated-measures ANOVA (with two factors: *Previous trial condition* (2 levels: VV–IV/II–VI) and *Electrodes*) were performed. VV–IV sequences were compared in the first ANOVA, and II–VI in the second one. The computing of two independent ANOVAs was due to the primary interest of the present report in comparing the processing of trials with the same validity condition, but preceded by trials with different/equal condition. If the results show ERPs differences in the comparisons VV vs IV or II vs VI, these variances must be attributed to the influence of previous trial condition.

In sum, the main objective of present study would be to analyze the possible ERP modulation effects generated by the *Previous trial condition* in the processing of the second trial target (Sequential Effect).

3. Results

3.1. Statistical analysis of Reaction Times

Previous studies showed a growth pattern on Reaction Times (RTs) (VV < IV < II < VI) (Arjona and Gómez, 2011, 2013; Jongen and Smulders, 2007; Gómez et al., 2009; Arjona et al., 2014). Present study is focused on ERPs analyzes; an exhaustive behavioral analysis of present data can be found in a previous publication (Arjona and Gómez, 2011).

3.2. Statistical analysis of event related potentials

Electrodes and time windows for each component were selected *a priori* based in our experience in this particular paradigm (see Figs. 4.3 and 4.4 in Arjona and Gómez, 2013), and the scientific literature about these components (Parasuraman, 1980; Woldorff et al., 1993; Näätänen et al., 1978; Näätänen and Michie, 1979; Alho et al., 1987; Mangun and Hillyard, 1991).

3.2.1. Auditory evoked potential (N1)

For the N1 time window (90–110 ms after the target onset), twenty-four electrodes were selected (F1, F2, FC1, FC2, C1, C2, CP1, CP2, F3, F4, FC3, FC4, C3, C4, CP3, CP4, F5, F6, FC5, FC6, C5, C6, CP5, CP6).

In the first analysis (VV–IV); ANOVA showed significant differences for *Previous trial condition* ($F(1, 28) = 5.49$, $MSE = 10$, $p < .026$, $SE = .16$) and *Electrodes* ($F(3.74, 104.8) = 26.97$, $MSE = 13.67$, $p < .001$, $SE = .49$). In the second analysis (II–VI); ANOVA showed significant differences for *Electrodes* ($F(3.95, 110.81) = 19.22$, $MSE = 17.89$, $p < .001$, $SE = .40$).

Results showed that the N1 component present an increased amplitude in the IV compared to the VV sequence (Fig. 2a).

3.2.2. P2 component

For the P2 time window (156–196 ms after the target onset), six electrodes were selected (FC1, FC2, C1, C2, CP1, CP2).

In the first analysis (VV–IV); ANOVA showed significant differences for *Previous trial condition* ($F(1, 28) = 13.24$, $MSE = 5.36$, $p < .001$, $SE = .32$) and the interaction *Previous trial condition x Electrodes* ($F(2.43, 68.13) = 4.23$, $MSE = .29$, $p < .013$, $SE = .13$). In the second analysis (II–VI); ANOVA showed significant differences for the interaction *Previous trial condition x Electrodes* ($F(2.67, 74.9) = 4.85$, $MSE = .85$, $p < .005$, $SE = .14$).

Results showed that the P2 component present an increased amplitude in the VV compared to the IV sequence (Fig. 2b).

The topographies of the amplitude differences (mean amplitude in VV sequence minus IV sequence) in the N1 and P2 components (right side of Fig. 2a,b) were, in both cases, fronto-centrally located. Fig. 3 shows these amplitude differences on both sides (FC1 and FC2) for targets in left and right ears. It can be observed that the effect of previous trial condition generated a continuous wave in the latency of N1 and P2 that could be interpreted as a PN (note that, in order to coincide with the topographies, the graphics in Fig. 3 show a PN with a positive polarity).

3.2.3. P3a component

For the P3a time window (260–300 ms after the target onset) eight electrodes (FC1, FC2, FC3, FC4, C1, C2, C3, C4) were selected.

The first ANOVA (VV–IV) showed significant differences for *Electrodes* ($F(3.58, 100.44) = 4.31$, $MSE = 4.54$, $p < .004$, $SE = .13$). The second ANOVA (II–VI) showed significant differences for *Previous trial condition* ($F(1, 28) = 7.28$, $MSE = 51.27$, $p < .012$, $SE = .20$), *Electrodes* ($F(3.34, 93.64) = 3.81$, $MSE = 7.49$, $p < .010$, $SE = .12$) and the interaction *Previous trial condition x Electrodes* ($F(3.44, 96.47) = 3.7$, $MSE = 1.56$, $p < .011$, $SE = .11$).

Results showed a higher P3a amplitude in the VI sequence than in the II sequence (waves and topographies in Fig. 4a and c).

3.2.4. Early P3b component

For the early P3b time window (260–300 ms after the target onset), four electrodes were selected (PO5, PO6, PO7, PO8).

The first ANOVA (VV–IV) showed not significant effects. Instead, the second analysis (II–VI) showed significant differences for *Previous trial condition* ($F(1, 28) = 9.07$, $MSE = 12.16$, $p < .005$, $SE = .24$) and *Electrodes* ($F(1.29, 36.38) = 4.32$, $MSE = 8.36$, $p < .035$, $SE = .13$).

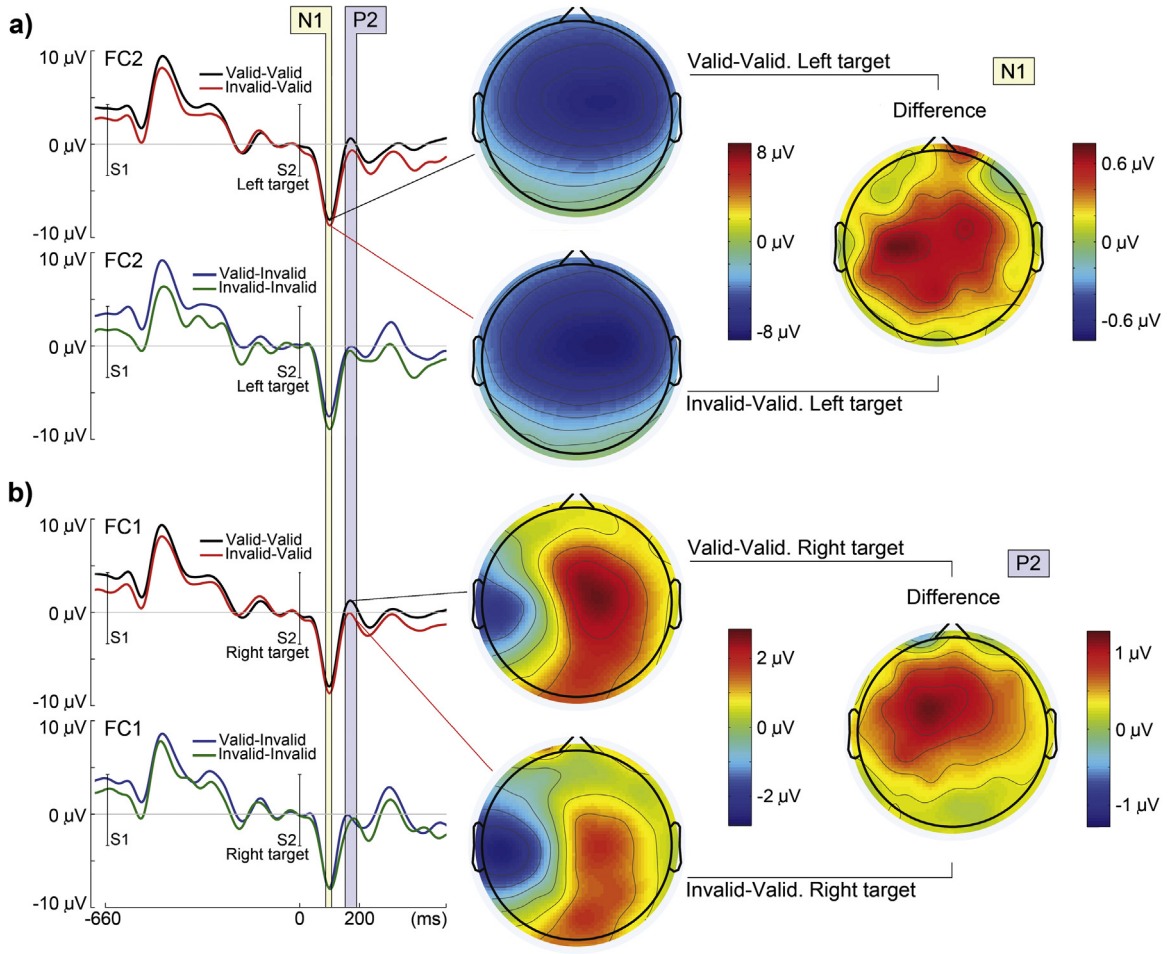

Fig. 2. Sequential effects in N1 and P2 components.
The waves and topographies in a and b show that both the N1 and P2 components presented higher negativity in valid trials preceded by invalid trials (IV) than in valid trials preceded by valid trials (VV). Both components showed this negativity after left and right targets, and it was probably due to the overlapping PN.

Results indicated that the P3b, at the early latency, present a higher amplitude in the VI than in the II sequence (waves and topographies of Fig. 4b and c).

3.2.5. Late P3b component

For the late P3b time window (310–350 ms after the target onset) four electrodes were selected (PO5, PO6, PO7, PO8).

In the first analysis (VV–IV), ANOVA showed a tendency toward significant effects for *Previous Trial condition* (F (1, 28) = 3.76, MSE = 2.59, p < .062, SE = .11). In the second analysis (II–VI), ANOVA showed significant differences for *Previous trial condition* (F (1, 28) = 15.84, MSE = 12.44, p < .001, SE = .36).

Results confirm that the late P3b present higher amplitude in the VI sequence than in the II sequence. They also suggest a tendency toward higher amplitude in the IV sequence compared to the VV sequence (waves and topographies of Fig. 4b and c).

4. Discussion

People are continuously generating *a priori* conditional probabilities for different cues (S1) as predictors of upcoming events (S2). These conditional probabilities (p (S2/S1)) would be continuously updated (based on previous cue-target outcomes) in order to adapt our behavior to the environment (Friston, 2009; Bruce and Tsotsos, 2009; Reynolds and Heeger, 2009; Feldman and Friston, 2010; Gómez and Flores, 2011).

The present study tries to analyze this cognitive-related dynamic modulation that would allow subjects to adapt their behavior to the continuous changes occurring in the environment. This adaptive mechanism is reflected in the ERP variation that occurs after the onset of each target. The two-trials sequence approach makes it possible to observe the neural processing for the expected and unexpected target stimuli as a function of previous trial outcome. Previous trial condition (valid/invalid) would influence the next trial processing of auditory targets (N1, P2, P3a and P3b).

4.1. Behavioral results

Subjects' response RTs to targets are faster in valid trials than in invalid trials (Validity–Invalidity Effect) (Posner, 1980). Furthermore, several studies have found a clear growth pattern in RTs as a function of previous trial condition (VV < IV < II < VI) (Inter-trial Validity–Invalidity Effect) (Gómez and Flores, 2011; Jongen and Smulders, 2007; Arjona and Gómez, 2011; Gómez et al., 2009). This pattern has been interpreted as being related to an increase in the preparation to respond, induced by cues preceded by valid trials. The behavioral results of present experiment have been described previously (Arjona and Gómez, 2011), showing the described RT pattern of VV < IV < II < VI. The complexity of the behavioral analysis precluded to present the sequential behavioral and ERPs results in a single report.

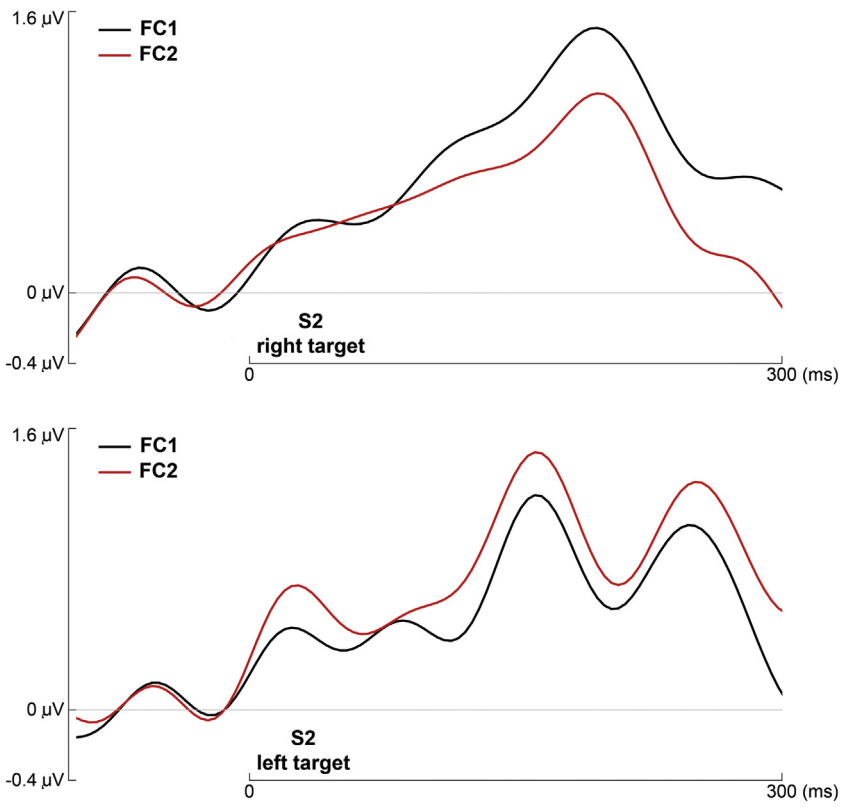

Fig. 3. Difference waves in the time range of the N1 and P2 components.
Both graphics represent the differences reflected in the topographies on the right side of Fig. 2a and b. The waves correspond to the combination of both hemispheres (FC1 and FC2) with the left and right target. These difference waves would reflect the influence of the PN on the N1 and P2 latency range. Note that, in order to coincide with the topographies, the graphics show a PN with a positive polarity.

4.2. Event-Related Potentials results

4.2.1. N1 and P2 components

The analyses show a higher amplitude of N1 in valid trials preceded by invalid trials (IV) compared to valid trials preceded by valid trials (VV) (Fig. 2a). By contrast, the P2 component presents higher positivity in valid trials preceded by valid trials (VV) compared to valid trials preceded by invalid trials (IV) (Fig. 2b). Based on the notion of PN, both components would be equally affected by this overlapping negative potential, increasing N1 and decreasing P2 in valid trials preceded by invalid trials (IV). In this sense, the difference waves (Fig. 3) showed continuity in the latency ranges of N1 and P2, suggesting the presence of this PN. It has been proposed that PN is an index of the attentional effort to process stimuli (Michie et al., 1990; Näätänen and Michie, 1979). Thereby, the higher amplitude of the PN in the IV sequence with respect to the VV sequence would suggest a more intense processing of valid targets preceded by invalid trials (IV). By contrast, valid targets preceded by valid trials (VV) would elicit less attentional processing due to the absence of a validity change. Interpretations from the predictive coding hypothesis indicate that targets in valid trials preceded by valid trials (VV) are more predictable than those preceded by invalid trials (IV) and would generate a lower N1 amplitude (Summerfield and de Lange, 2014). However, the presence of a classic PN extending on N1 and P2 latencies, suggest that the attention effort in IV must also be a component to interpret the reduction of N1 amplitude in the VV sequence with respect to IV sequence. In this sense, the increased PN in IV sequences, compared to VV sequences, would be a consequence of the higher CNV and LRP induced by the cue in trials preceded by a valid trial, compared to trials preceded by an invalid trial. Using the same records presented in this report, we previously showed this effect of the CNV and LRP (Arjona and Gómez 2013; Arjona et al., 2014). The lower preparation in valid trials preceded by an invalid trial (IV sequences) would produce greater attentional effort, compared to VV sequences, to select the auditory target, as obtained in the PN.

On the other hand, no significant effects were obtained in the comparison II vs VI for the N1 and P2 components. The lack of statistical significance in the second hypothesis about N1 and P2 was probably due to a low signal-to-noise ratio in the comparison VI vs II given the low number of II trials and the small size effects in the N1 and P2 comparisons. Please notice that small size effects are expected given that the sequential effects refer to ERPs modulation after auditory target in trial n generated by the cue-target combination in trial n – 1.

4.2.2. P3a and P3b components

Results showed a higher P3a and P3b in invalid trials preceded by valid trials (VI) compared to invalid trials preceded by invalid trials (II). This increase would indicate a greater surprise generated by the target in the VI sequence, compared to the II sequence, requiring more attentional reorientation (P3a) and working memory updating (P3b). The working memory updating would be originated by the evaluation of the incongruity between the preparation generated by the cue and the target location in the invalid trials (P3b) (Gómez and Flores, 2011; Mangun and Hillyard, 1991). The obtained data may be interpreted as if the invalid trials preceded by valid trials are experienced as more unexpected than the invalid trials preceded by invalid trials, and require a higher updating of the p(S2/S1). In this line, it must be indicated that, in CCPP, invalid trials generate a higher P3a and P3b amplitude than valid trials (Mangun and Hillyard, 1991; Gómez and Flores, 2011), and the higher P3b amplitude in invalid trials would be a function of cue validity value (Arjona and Gómez, 2016).

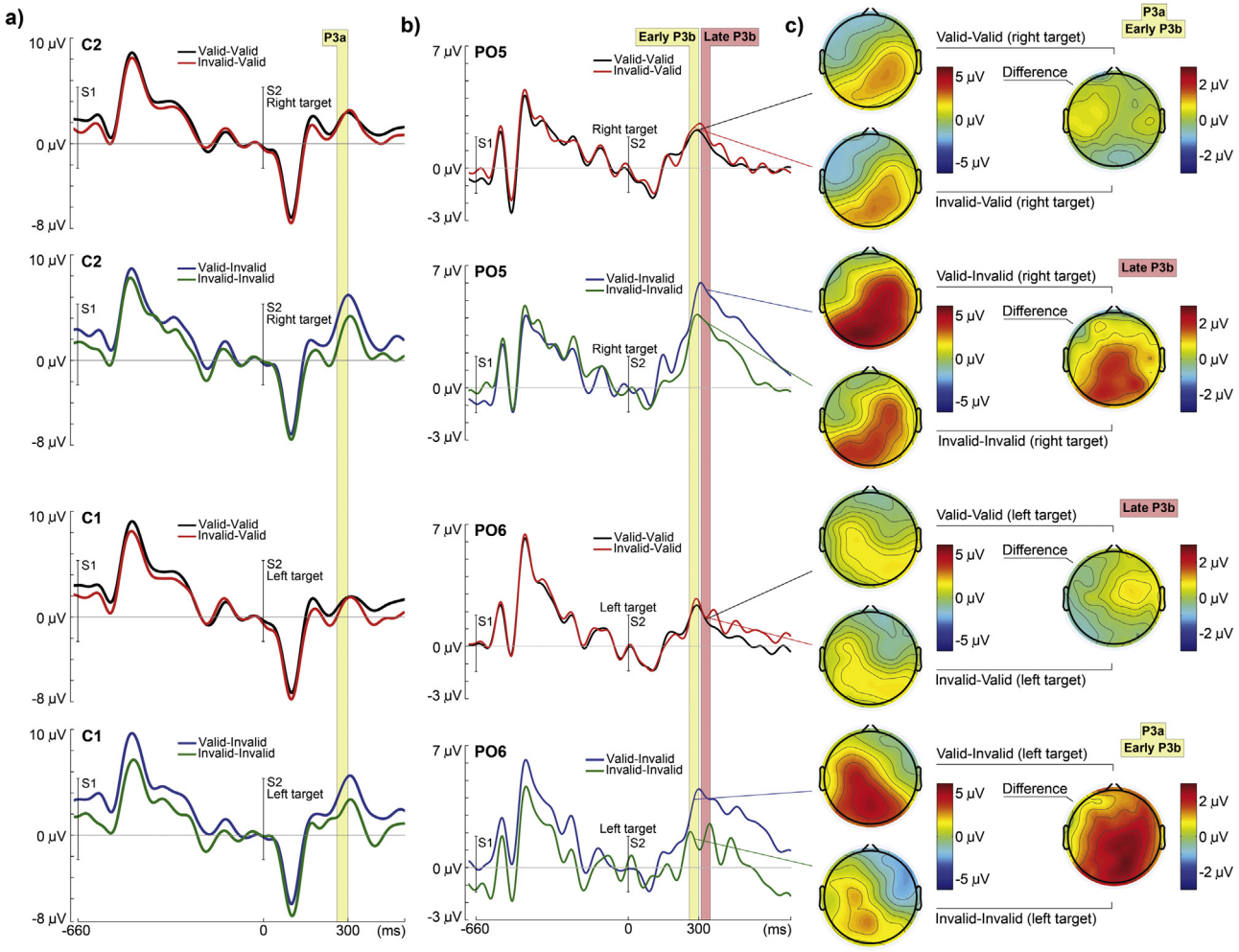

Fig. 4. Sequential effects in the P3a and P3b components.
The waves and topographies show that the P3a and P3b (early and late) components present higher positivity in invalid trials preceded by valid trials (VI) compared to invalid trials preceded by invalid trials (II). a represents the waves in P3a, b represents the waves in P3b (early and late), and c represents the topographies in both components.

The present results add evidence to the concept that P3a and P3b components indexes neural activity related to the processing of prediction error: the difference between the expected and the outcome of current trial. In this line, it has been proposed that P3b indexes the predictive surprise, related to the likelihood of events, and P3a indexes the Bayesian surprise, related to the belief updating induced by the divergence between prior and posterior beliefs (Kolossa et al., 2015; Seer et al., 2016). The obtained increase of P3a in present experiment would then be related to the change in the credibility assigned to the cue, which would be higher in the VI than in the II sequence. Regarding to P3b, the increase in VI with respect to II sequence, would suggest that, in the particular conditions of present experiment, this component participates in the modification of the predictive value of the cue in an inference-based mode. These results are compatible with Seer et al. (2016), given that the increase of P3b amplitude generated by rare events was lower in situations in which learning was guided by inferences than when it was guided by the frequency of the events, but the fact that P3b was still significant in inference based learning, suggests that P3b also participates in the process of inference based adaptation. Another concept that would fit the present P3b results is the Local/Global Probability effect (Duncan-Johnson and Donchin (1982); Picton, 1992). In this phenomenon, the amplitude of a P3b induced by a target is a function of the global and local target frequency. Along the same lines, block-probability variations (global probability) in CCPP have been shown to change the P3b amplitude in invalid trials (50% < 68% < 86%) (Arjona et al., 2016). Regarding the present experiment, the local probability effect would be influencing the P3b modulation (II < VI and a statistical trend for VV < IV). However, rather than just being interpreted as an effect of the local probability of targets, which is a frequent approach, the presence of cues before targets, inducing a CNV in the cue-target period (Arjona and Gómez, 2013), allows us to suggest that the previous trial condition is changing the subjective local probability of the expected location of targets.

We recently proposed that the CNV would not only be related to the attentional set for the next stimulus, but also to inferences about the characteristics of the next stimulus (in this case the location of the auditory target) (Arjona et al., 2016). In this schema, when the target appears in the invalid position, the violation of the expectations would produce a prediction error, which generates a higher P3b amplitude if the target is more expected (VI sequences) than if it is less expected (II sequences). The CNV (higher in trials preceded by a valid trial than in trials preceded by an invalid trial) would index not only the activation of the neural representation of the expected location of the target, but also the associated conditional cue-target probability, and the P3b would be coding for the violation of the expected location (I > V) and for the associated expected likelihood that the target would appear at a certain location in the next trial (VI > II).

Finally, the comparison IV vs VV only induced a statistical significance trend. This lack of significant results is probably due to the global effect (80% validity/20% invalidity), which would induce in the subject a high credibility for the cue, irrespectively of the outcome of previous trial.

5. Conclusions

The present results confirmed two of the initial hypotheses: (i) a higher PN will be obtained in the IV sequence, compared to the VV sequence, given that, in both sequences, the second target is attended to, but the IV sequence needs extra attentional effort (due to the lower credibility of the cue after an invalid trial) in the processes of orientation and perception of the auditory target. Additionally, an influence of the higher predictability of targets in VV with respect to IV sequences would justify the lower amplitude of N1 in the VV sequences; (ii) an increase in the P3a and P3b amplitude will be observed in the VI sequence, compared to the II sequence, due to the higher processing of the unexpected invalid target after a valid one. This processing would correspond to the updating of the conditional probabilities (p(S2/S1)) and would be in the line of previous studies showing changes in RTs and CNV generated by the outcome of previous trial (Jongen and Smulders, 2007; Arjona and Gómez, 2011, 2013; Arjona et al., 2014).

The obtained results would fit the concept of Bayesian Processing (Friston, 2010); in which neural responses are continuously influenced by previous trial outcome, and support the role of late positivities in the updating process (Kolossa et al., 2015; Seer et al., 2016).

Acknowledgement

This work was supported by the Ministry of Science and Innovation [PSI2013-47506-R].

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