Relations entre conscience et représentations sémantiques verbales : approche comportementale et neurophysiologique chez le sujet sain et le patient cérébro-lésé

Benjamin Rohaut

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Relations entre conscience et représentations sémantiques verbales :

Approche comportementale et neurophysiologique chez le sujet sain et le patient cérébro-lésé

Par Benjamin Rohaut

Thèse de doctorat de Neuroscience

Dirigée par Lionel Naccache

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Devant un jury composé de :

Pr. Jacques Luauté,	Professeur des Université (UCBL)	Rapporteur
Dr. Fabien Perrin,	Maître de conférences (UCBL)	Rapporteur
Pr. Louis Puybasset,	Professeur des Université (Paris VI)	Examinateur
Pr. Lionel Naccache,	Professeur des Université (Paris VI)	Directeur

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Sommaire

Introduction

Comment attribuons-nous un sens à une perception ? Comment identifions-nous un objet, un mot ? Comment comprenons-nous plus généralement le monde qui nous entoure? Parmi les différentes modalités sensorielles dont nous disposons, c'est le traitement de l'information visuelle qui a été le plus étudié. L'identification d'un objet comme par exemple un visage ou un mot écrit ne prend que quelques dizaines de millisecondes : après que le cortex visuel primaire a codé des paramètres de bas niveaux tel que l'orientation des lignes, les contrastes, les couleurs ou les volumes, des régions hyperspécialisées[1] identifient l'objet relativement à ce qui est « déjà connu ». Cette connaissance, stockée en mémoire et relative à l'objet perçu, peut alors être « accédée ». Cet accès à la connaissance relative à une perception correspond à ce que l'on appelle généralement le « traitement sémantique ».

Cependant parmi l'énorme quantité d'information qui nous inonde, seule une faible partie accède à notre conscience. Une très grande part des processus impliqués dans le traitement des informations sensorielles a en effet lieu de manière « automatique »[2], non consciente. Nous verrons dans cette thèse que les bases neurales de la conscience et du traitement sémantique sont extrêmement intriquées. Nous verrons aussi que si certains niveaux de traitement sémantiques peuvent opérer de manière automatique et non consciente, d'autres semblent requérir un accès conscient.

En plus de son intérêt scientifique fondamental, ces travaux sur la caractérisation des différences entre traitement sémantique conscient et non conscient ouvrent des perspectives intéressantes en termes d'exploration des capacités résiduelles de fonctionnement cérébral de patients non communicants ou affectés d'un trouble de la conscience. Ces explorations pourraient en effet permettre des avancées majeures à la fois diagnostiques, pronostiques et thérapeutiques.

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[1] Comme l'aire visuelle des visages du gyrus fusiforme ou l'aire de la forme visuelle des mots du gyrus fusiforme postérieur gauche par exemple

[2] Nous reviendrons sur cette caractérisation classique des traitements non conscients

1 La sémantique

1.1 Généralités

La « sémantique », telle qu'elle est définie dans un dictionnaire, correspond à la branche de la linguistique s'intéressant à l'étude du sens des mots (« sémantique » vient du grec ancien « σημαντικός » soit « sêmantikós » ou « significatif »)[3]. Mais en neurologie et en neuroscience, lorsque l'on parle de traitement sémantique, on fait plus le plus souvent référence aux mécanismes cérébraux permettant l'accès au sens et plus généralement à la connaissance. Cette connaissance est stockée dans une mémoire que l'on appelle la « mémoire sémantique ».

La mémoire sémantique contient tout notre savoir relatif aux objets (concrets ou abstraits) du monde qui nous entoure. L'accès à ce savoir constitue un processus cognitif qualifié de sémantique. Ce savoir est à la base de presque toutes les activités humaines pourtant, ses bases neurobiologiques commencent à peine à être connues. Nous verrons que l'accès à cette connaissance implique non seulement des régions dites « associatives » multimodales, mais également des régions unimodales sensorielles et motrices.

Le terme de « sémantique » n'ayant finalement pas de définition univoque, il est utile de définir le sens qu'on lui accordera dans cette thèse : nous utiliserons le terme de « traitement sémantique verbal» ou plus simplement de « traitement sémantique» pour désigner les mécanismes cérébraux permettant l'accès au sens et à la connaissance (stockée dans la mémoire sémantique) de matériel verbal : les mots.

1.2 Le « savoir » et la mémoire sémantique

1.2.1 La mémoire sémantique

Un cerveau humain adulte possède en mémoire une multitude d'informations (ou connaissances) concernant les concepts relatifs au monde qui l'entoure. Ce savoir acquis progressivement tout au long de la vie, constitue ce que l'on appelle la mémoire sémantique.

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[3] Exemples de définitions issues de dictionnaire grand public: « L'étude du sens des unités linguistiques et de leurs combinaisons » (Dictionnaire Larousse), «L'étude de la signification des mots » (Wikipédia).

Il contient par exemple la connaissance des noms, des attributs physiques, de l'origine et de l'histoire des objets concrets. Il comprend aussi les connaissances relatives aux concepts abstraits, aux actions et comportements, aux relations causes / effets, etc…

Une grande variété de comportements humains repose sur ce savoir conceptuel comme par exemple la reconnaissance et l'utilisation d'objets, la capacité d'appréhender des concepts abstraits, de les manipuler entre eux, de les nommer et ainsi de les partager avec autrui. Toutes les cultures humaines, qu'elles soient scientifiques, littéraires, religieuses, artistiques, ou autre sont construites autour d'un socle de savoir conceptuel de ce type. Nous ne pouvons pas raisonner, nous remémorer le passé ou imaginer l'avenir sans accéder à ce savoir. Pour autant, si cette mémoire est impliquée dans quasiment toutes les activités humaines, ses bases neurobiologiques commencent à peine à être connues.

La mémoire sémantique contient des connaissances non nécessairement liées à une expérience perceptuelle immédiate ou remémorée. On considère qu'il s'agit d'un savoir conceptuel (Tulving, 1972). La mémoire liée à des expériences perceptuelles passées est généralement appelée mémoire épisodique[4]. Un tel modèle de stockage conceptuel de l'information (en comparaison à un stockage symbolique) présente l'avantage majeur de permettre l'élaboration plus facile d'un modèle biologique d'apprentissage de nouveaux concepts : à la faveur d'expériences sensorielles similaires avec des « entités » appartenant à une même catégorie conceptuelle, une représentation sensorielle (ou motrice) idéalisée peut émerger via un phénomène de généralisation au travers de ces exemples uniques. La réactivation ou la « simulation »[5] de ces représentations sensorielles serait à la base de la réactivation conceptuelle (Tulving, 1972). Un tel modèle répond par ailleurs mieux au principe de parcimonie puisque une même représentation sensorielle peut être utilisée pour différentes représentations conceptuelles.

Chaque « entrée » dans la mémoire sémantique peut activer un réseau plus ou moins étendu de connaissances, ainsi par exemple la vision d'un lapin ou du mot « lapin » n'implique pas forcément uniquement l'évocation (comme dans un dictionnaire) du « petit mammifère à grandes oreilles mangeur de carottes » mais possiblement un champ de connaissance

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[4] La distinction entre mémoire épisodique et mémoire sémantique est néanmoins sujette à débat, on peut en effet voir la mémoire épisodique comme une forme de manipulation particulière du savoir contenue dans la mémoire sémantique en le replaçant dans un espace spatio-temporel défini, voir 1.2.2.

[5] On entend ici par « simulation » le fait de générer une représentation mentale sans objet, on parle aussi souvent d'imagerie mentale.

beaucoup plus vaste (plus semblable à l’arborescence d’une recherche internet), en partie variable d’un individu à l’autre. Ce champ de connaissances pourra par exemple concerner le souvenir du plat des jours de fêtes de votre grand-mère, le Bugs Bunny des cartoons, un des nombreux tabous des marins d’autrefois, etc…(voir Figure 1). Le champ de ce réseau pourra par ailleurs être variable en fonction du contexte, qu’il s’agisse d’influences externes (influences *bottom-up*) ou de la posture consciente (influence *top-down*) dans lequel l’accès au concept a lieu[6].

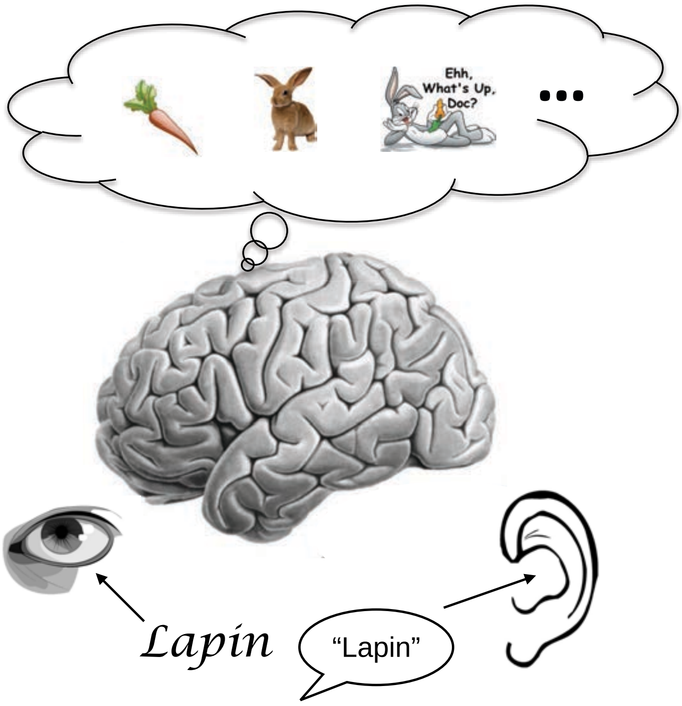

Figure 1. Représentation schématique d’un traitement sémantique verbal

L’accès au concept relatif à la lecture ou l’écoute d’un mot (par exemple « lapin ») peut « activer » des représentations conceptuelles liées (par exemple « carotte », « Bugs Bunny » etc...).

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[6] Les moteurs de recherche internet essayent d’utiliser ce type de contextualisation pour personnaliser les résultats proposés.

1.2.2 Les autres types de mémoire

Plusieurs modèles concernant l’organisation de la mémoire chez l’homme ont été proposés depuis le début du XIX^{ème} siècle. On y distingue habituellement la mémoire explicite (verbalisable, comme par exemple la forme d’un objet qui peut facilement être décrite) de la mémoire implicite (non verbalisable, comme par exemple un schéma moteur). La mémoire explicite est elle-même le plus souvent divisée en deux : la « mémoire sémantique » qui nous intéresse ici et qui, comme nous l’avons déjà vu, concerne les connaissances générales du monde (Bréal, 1904) et la mémoire dite épisodique, liée à l’histoire personnelle du sujet (remémoration d’épisodes de la vie, chronologie, etc… ; Figure 2).

Ces divisions, bien que sous-tendues en partie par certaines observations de dissociations neuropsychologiques chez des patients présentant une pathologie de la mémoire, sont cependant aussi en partie théoriques. Ces différents types de mémoire sont probablement en réalité intimement liés au sein d’un vaste réseau (Squire, 2004). Deux méta-analyses récentes retrouvent par exemple la mise en jeu d’un réseau cérébral très similaire au cours de tâches

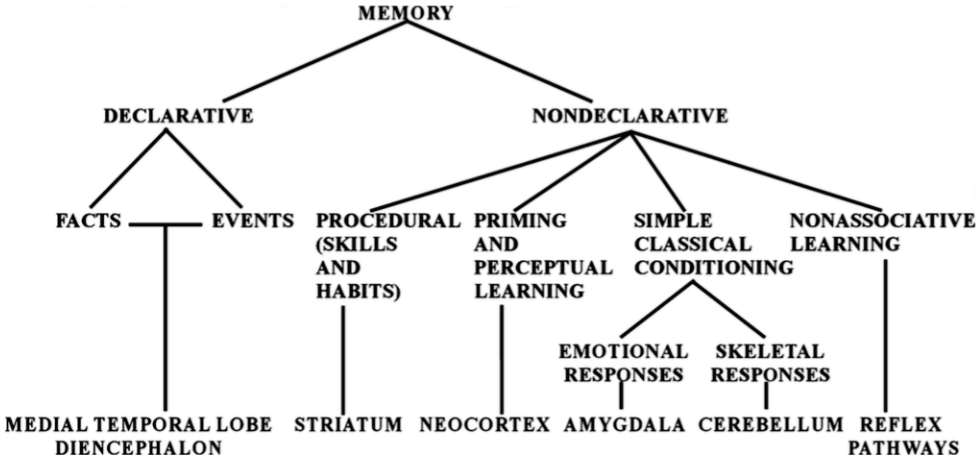

Figure 2. Représentation schématique des différents types de mémoire chez l’homme

Dans un tel modèle la mémoire sémantique correspond à la mémoire déclarative relative aux faits (facts). Adapté de Squire Neurobiol Learn Mem 2004.

impliquant la mémoire sémantique et la mémoire autobiographique (Svoboda, McKinnon, & Levine, 2006; Binder, Desai, Graves, & Conant, 2009). On peut par ailleurs remarquer qu'avec le temps, un souvenir autobiographique peut devenir « sémantique » par perte de sa contextualisation.

1.2.3 Bases neurobiologiques de la mémoire sémantique

Les données récentes de la neuro-imagerie ont permis de mieux cerner les bases neurobiologiques de la mémoire sémantique. Ces études explorent les régions cérébrales activées lors de l'accès au sens d'un objet en contrastant des conditions dans lesquelles la mise en jeu de la mémoire sémantique doit être le seul facteur variable. Un des contrastes les plus simples consiste à comparer les activations faisant suite à la lecture ou à l'écoute de mots, à celles obtenues avec des pseudo-mots (non-mots prononçables, respectant les règles orthographiques mais dépourvues de sens comme par exemple « breluche »). Un certain nombre de critères lexicaux doivent cependant être contrôlés afin que les différences observées ne reflètent bien que l'aspect sémantique (fréquence des couples et triplets de lettres, forme orthographique, fréquence des syllabes etc…). Ces études et notamment une méta-analyse regroupant 120 études mettent en avant le rôle des régions sensori-motrices unimodales en plus des régions multimodales associatives (Binder & Desai, 2011).

1.2.3.1 Rôle des régions corticales sensori-motrices unimodales

Dès le XIX$^{\text{ème}}$ siècle, certains neurologues supposaient déjà que l'accès au sens d'une perception pouvait nécessiter, au moins dans une certaine mesure, l'activation de régions unimodales sensorielles, notamment les cortex visuel, auditif et sensori-moteur (Wernicke, 1874; Freud, 1891). Ils avaient en effet remarqué que certains patients présentant une lésion au niveau de régions cérébrales impliquées dans la motricité comme par exemple la maladie de Parkinson (Boulenger et al., 2008), la paralysie supra-nucléaire progressive (Bak et al., 2006), la sclérose latérale amyotrophique (Bak & Hodges, 2004; Grossman et al., 2008) ou présentant un déficit de la programmation du mouvement (apraxie) (Buxbaum & Saffran, 2002) pouvaient présenter un déficit de compréhension des verbes d'action.

Plus récemment, Binder & Desai (2011) ont pu montré en reprenant les résultats de 38 études, l'implication des régions corticales sensorielles unimodales dans l'accès au sens de matériel verbal (Figure 3). Ainsi par exemple l'accès au sens de mot en relation avec un mouvement, une couleur, un son ou une émotion s'accompagne respectivement d'activations au niveau du cortex impliqué dans le traitement de ce type d'information : temporal inférieur (mouvement), gyrus fusiforme (couleur), temporal supérieur (son), pôle temporal et cortex préfrontal ventromédial (émotion).

La question de la relation causale de ces activations a fait débat: pour certains elle pouvait n'être que secondaire à l'activation première d'un concept (imagerie mentale). Finalement le rôle causal des régions sensori-motrices dans le traitement sémantique, suggéré par certains déficits sélectifs dans les pathologies sus-citées, a pu être étayé par des études neurophysiologiques. Plusieurs travaux ont en effet montré qu'il s'agissait d'un évènement survenant de manière précoce dans la cascade du traitement sémantique. L'activation du cortex moteur au cours du traitement d'un verbe d'action survient par exemple entre 150 et 200 ms, suggérant bien qu'il ne s'agit pas d'un épiphénomène mais bien d'une partie intégrante du processus permettant l'accès au sens du mot (Boulenger et al., 2006; Hoenig, Sim, Bochev, Herrnberger, & Kiefer, 2008; Pulvermüller, Shtyrov, & Ilmoniemi, 2005; Revill, Aslin, Tanenhaus, & Bavelier, 2008).

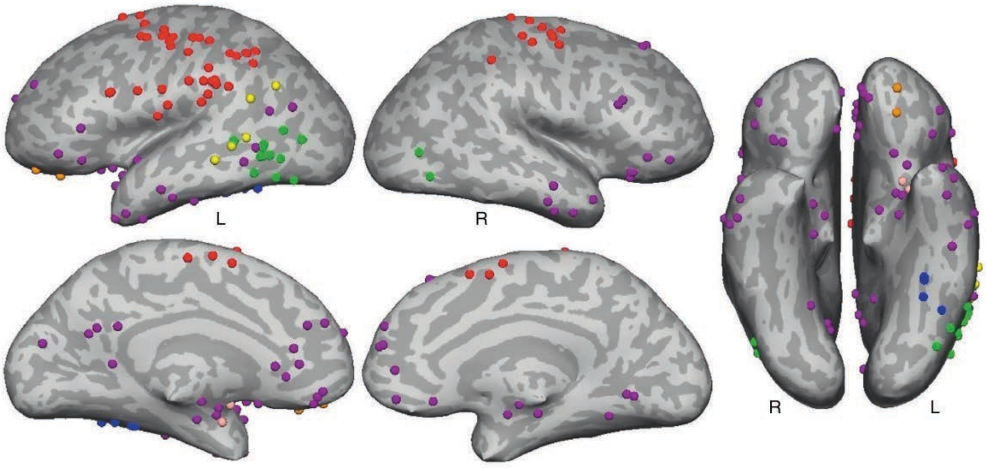

Figure 3. Régions unimodales impliquées dans le traitement sémantique

Méta-analyse de 38 études d'imagerie fonctionnelle identifiant les principaux foyers d'activations dans les régions corticales unimodales au cours de l'accès au sens de mots selon leur contenu sensoriel (action: rouge ; son: jaune ; couleur : bleu ; émotion: violet ; mouvement : vert ; odeur: rose ; goût: orange). Adapté de Binder & Desai. TICS 2011.

1.2.3.2 Rôle des régions corticales multimodales « associatives »

A la fin des années 80, Antonio Damasio a formalisé une théorie de l'accès sémantique selon un modèle « hiérarchique distribué » (Damasio, 1989). Dans ce modèle, les grandes parties du cortex cérébral constituées de régions dites « associatives», situées entre les régions unimodales perceptives, apparaissent comme des « zones de «convergence » permettant l'accès à des « représentations abstraites ». Ces régions multimodales ont également été mises en évidence dans la méta-analyse de Binder & Desai (2011) et comprennent le cortex pariétal inférieur (gyrus angulaire et supramarginal), le gyrus temporal inférieur et moyen, et la partie antérieure du gyrus fusiforme. D'autres régions multimodales

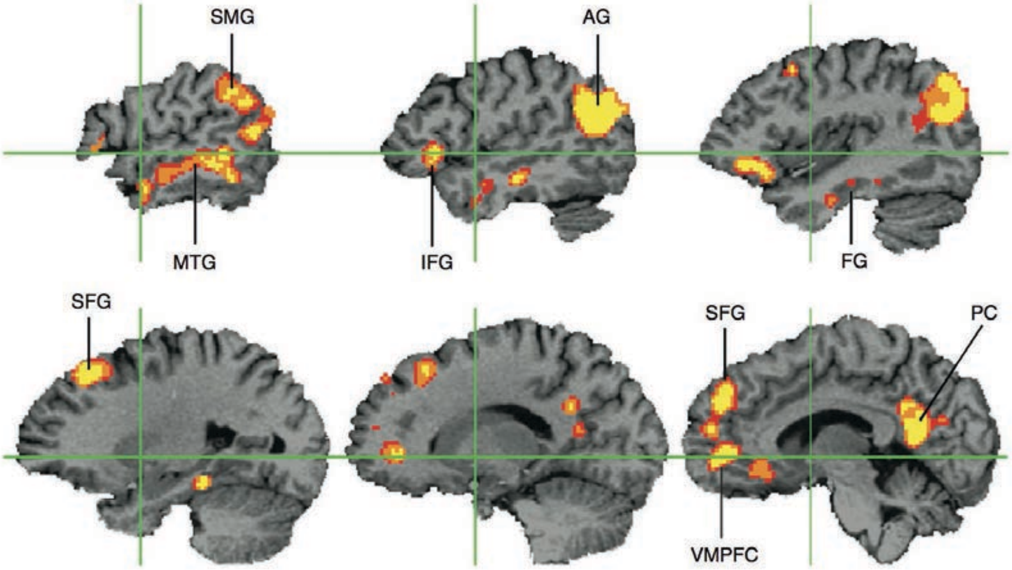

Figure 4. Régions multimodales impliquées dans le traitement sémantique

Méta-analyse de 120 études d'imagerie fonctionnelle identifiant les principaux foyers d'activations dans les régions corticales multimodales au cours de l'accès au sens de mots (AG = angular gyrus, FG = fusiform gyrus, IFG = inferior frontal gyrus, MTG = middle temporal gyrus, PC = posterior cingulate gyrus, SFG = superior frontal gyrus, SMG = supramarginal gyrus, VMPFC = ventromedial prefrontal cortex. Adapté de Binder & Desai. TICS 2011.

seraient impliquées : cortex préfrontal dorsomédial et ventromédial, gyrus frontal inférieur,cortex cingulaire postérieur et précuneus (Figure 4). Patterson (2007) souligne de son coté le rôle central du pôle temporal en tant que zone de convergence (il parle de *hub*), essentiellement du fait de l'observation de patients atteints de démence sémantique chez lesquels les lésions prédominent effectivement à ce niveau.

Cette convergence permettrait à nos expériences perceptuelles d'accéder à un niveau de représentation abstrait, autorisant une variété de fonctions conceptuelles telle que la reconnaissance d'objet, la cognition sociale, le langage et la capacité remarquable du cerveau humain de pouvoir se remémorer le passé et imaginer le futur.

1.2.3.3 Importance relative et relations entre régions uni et multimodales

Plusieurs théories proposent une séparation variable entre représentations perceptuelles et conceptuelles (Figure 5). Les modèles « désincarnés » (*Disembodied*) sont souvent critiqués car ils impliqueraient l'existence d'une pensée purement abstraite, dépourvue de tout contenu perceptuel. Il semble en effet, que même pour les concepts les plus abstraits, il existe au moins dans une certaine mesure certains percepts. Par ailleurs les observations cliniques et les données de la neuro-imagerie précédemment citées vont contre ce type de modèle (Fodor, 1975; Pylyshyn, 1984; Mahon & Caramazza, 2008). A l'opposé on trouve les modèles de « forte incarnation » (*Strong embodiment*) dans lesquels les processus perceptuels et conceptuels seraient traités dans un même et vaste système. Ces modèles ne permettent pas de rendre compte des activations modalité-spécifiques mises en évidence par la neuro-imagerie ni des déficits sélectifs observés en clinique en cas de lésion des systèmes sensori-moteurs par exemple (Barsalou, 1999; Gallese & Lakoff, 2005). D'autres modèles « basés sur l'interaction » (*Grounding by interaction*) proposent que les représentations conceptuelles et perceptuelles soient séparées mais interagissent entre elles de telle manière qu'une représentation amodale puisse dans certains cas conduire à une expérience perceptuelle (Damasio, 1989; Patterson, Nestor, & Rogers, 2007; Rogers & McClelland, 2004). Patterson qui défend un modèle de ce type insiste sur le rôle central (le *hub*) que joueraient les pôles temporaux qu'il considère comme la principale zone de convergence (Patterson et al., 2007). Enfin le modèle « d'abstraction incarnée » (*Embodied abstraction*), défendu par Binder & Desai, semble être actuellement celui qui rend le mieux compte des données de la clinique et de la neuro-imagerie. Dans ce modèle les représentations conceptuelles consisteraient en de multiples niveaux d'abstraction allant des régions perceptives jusqu'aux régions associatives. Ces différents niveaux seraient activés de façon variable selon le contexte et non de manière automatique (Taylor & Zwaan, 2009; Dove, 2010; Binder & Desai, 2011). Ainsi une représentation abstraite pourrait prendre des formes variables de représentation plus concrète au gré des activations modales qui s'y associent, en fonction du contexte.

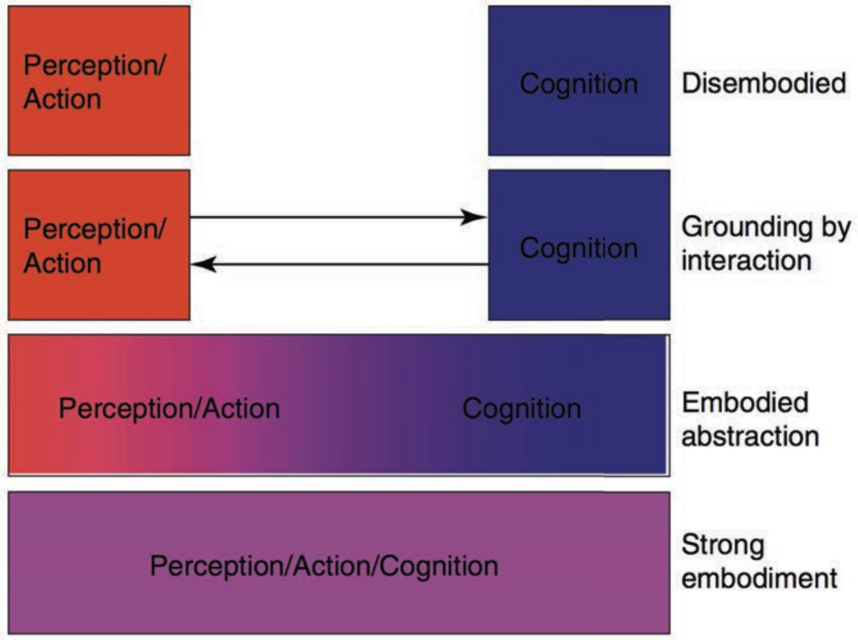

Figure 5. Relations possibles entre représentations perceptuelles et conceptuelles

Les données neuroanatomiques actuelles sont en faveur du modèle d'abstraction incarnée (Embodied abstraction) dans lequel les représentations conceptuelles consisteraient en de multiples niveaux d'abstraction allant des régions perceptives jusqu'aux régions associatives. Ces différents niveaux seraient activés de façon variable selon le contexte et non de manière automatique Adapté de Binder & Desai. TICS 2011.

Dans le modèle de Binder & Desai, des représentations modalité-spécifiques localisées près des réseaux de traitement correspondants (sensori-moteurs et émotionnels) émergeraient au gré de nos expériences perceptuelles répétées avec des objets similaires, réalisant un processus de généralisation (Figure 6, zones jaunes). Ces représentations coderaient les dimensions spatiales et temporelles récurrentes au niveau des modalités inférieures. Ce système correspondrait aux « zones de convergences locales » de Damasio (1989) et au « système unimodal de percept symbolique » de Barsalou (1999) En plus des afférences

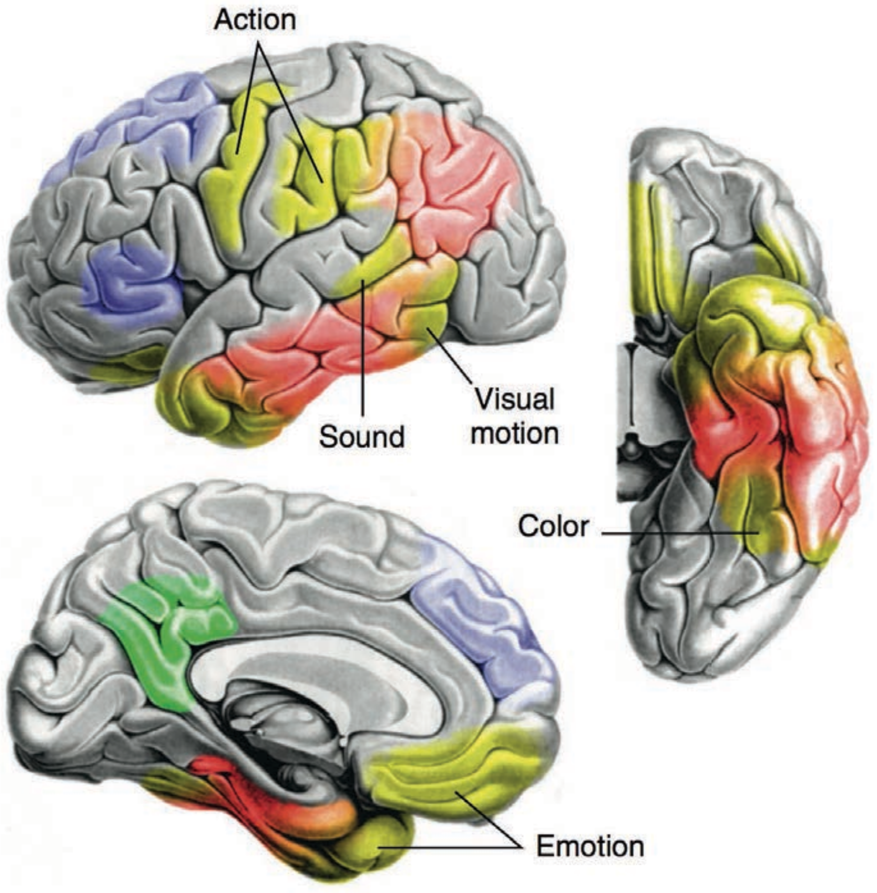

Figure 6. Exemple de modèle neuroanatomique du traitement sémantique

Les régions unimodales traitant les informations sensorielles, motrices et émotionnelles (en jaune) fournissent des informations perceptives aux régions multimodales (cortex temporal et pariétal inférieur, en rouge) stockant des informations de plus en plus abstraites. Le cortex préfrontal (dorsomédian et inférieur, en bleu) exerce un contrôle sur la sélection de l'information accédée en fonction du contexte (influences top-down). Le gyrus cingulaire postérieur et le précuneus (en vert) pourraient jouer un rôle d'interface avec la mémoire hippocampique (encodage en mémoire sémantique). Ces structures sont bilatérales bien que semblant prédominer du côté de l'hémisphère dominant Adapté de Binder et al. TICS 2011.

externes (*bottom-up*) dans leur modalité respective, ces modules pourraient recevoir des afférences (*top-down*) en provenance d'autres modalités et du système attentionnel. Ces zones de convergence modales convergeraient alors vers les régions associatives pariétales et temporales de plus haut niveau d'abstraction (Figures 6 zones rouges). Une des fonctionsprincipales de ces régions serait alors d'assurer la liaison entre les régions modales (ce que l'on appelle communément le *binding*) en liant par exemple la représentation mentale d'un miaulement de chat à son image visuelle et éventuellement à d'autres savoirs liés (Binder & Desai, 2011). De telles représentations supramodales seraient à même de pouvoir capturer des similitudes en termes d'attributs, permettant ainsi de catégoriser de la même manière une poire et un ananas, et ce en dépit de leur forme différente. Inversement une poire sera catégorisée différemment d'une ampoule et ce, malgré leur ressemblance. Ces deux systèmes modaux et supramodaux constitueraient le réseau de stockage de la mémoire sémantique alors que les régions préfrontales (en bleu) en contrôleraient les afférences *top-down*.

1.3 Le traitement sémantique verbal

Nous avons défini plus haut un « traitement sémantique verbal » comme l'ensemble des mécanismes cérébraux permettant l'accès au sens et à la connaissance (stockée dans la mémoire sémantique) du matériel verbal considéré. En effet, qu'il soit lu ou entendu, un mot, en tant que représentation symbolique relative à un objet (concret ou abstrait), constitue une « entrée » de la mémoire sémantique, au même titre que n'importe quel autre stimulus.

La façon dont est décodée cette information verbale, notamment le décours temporel des évènements se succédant jusqu'à l'accès au sens (ou à l'« idée ») d'un mot ainsi que leurs corrélats neuronaux respectifs, constitue une vaste question à laquelle il est encore aujourd'hui difficile de répondre avec précision. La linguistique, qui est la branche des sciences étudiant le langage à tous ses niveaux (phonologie, morphologie, orthographe, lexique, syntaxe, sémantique), distingue schématiquement deux grands modèles: le modèle sériel (ou séquentiel) et le modèle parallèle :

- Dans le modèle sériel, chaque étape du traitement de l'information verbale est réalisée par un module neuronal spécialisé et chacune de ces étapes se suit dans un ordre temporel établi : traitement phonologique / orthographique, lexical, syntactique puis sémantique, éventuellement suivi par une seconde analyse syntactique.

- Dans le modèle parallèle, ces différents niveaux d'analyse peuvent être engagés pour une large part de manière simultanée, précoce et parallèle par les différents modules neuronaux impliqués puis également suivis d'une étape de « ré-analyse » tardive optionnelle (Figure 7).

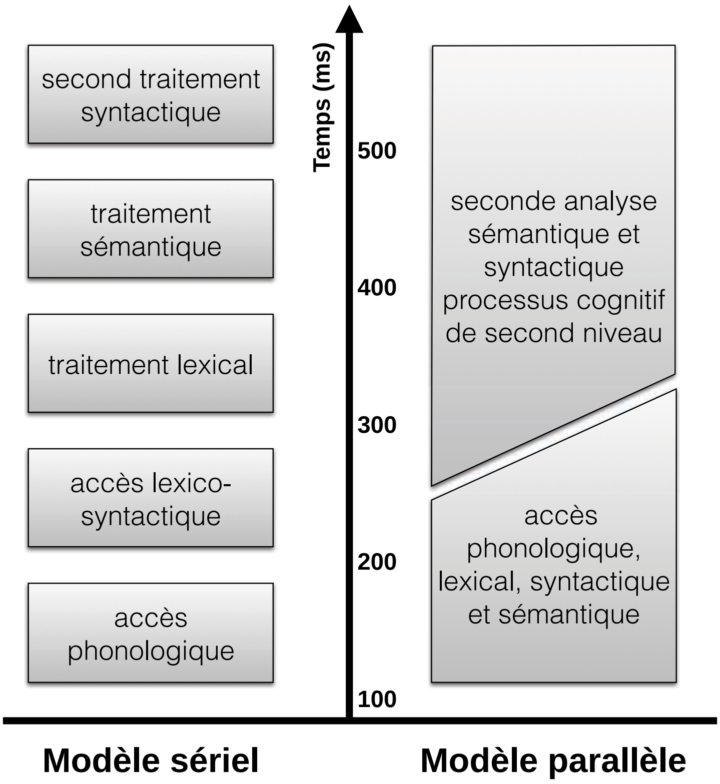

Figure 7. Modèle sériel et parallèle du traitement sémantique verbal

Dans le modèle sériel, chaque étape du traitement de l'information verbale est réalisée par un module neuronal spécialisé et chacune de ces étapes survient selon un ordre temporel établi. Dans le modèle parallèle, ces différents niveaux d'analyse peuvent être engagés pour une large part de manière simultanée, précoce et parallèle par les différents modules neuronaux impliqués suivis d'une étape de « ré –analyse » tardive optionnelle. Adapté de Pulvermüller, Brain Lang 2009.

Comme nous l’avons déjà vu avec l’exemple du « lapin », l’activation d’une représentation stockée en mémoire sémantique « déborde » généralement sur des concepts qui lui sont proches (par exemple « carotte »). L’accès éventuel à une de ces représentations « pré-activée » est alors rendu plus « facile ». Ce phénomène appelé « amorçage sémantique » (ou *priming* sémantique) est très utile car il permet de sonder l’accès au sens d’un mot en mesurant l’effet d’amorçage qu’il exerce sur une représentation voisine. Ainsi si l’on demande à un sujet d’effectuer une tâche nécessitant un accès sémantique sur le mot carotte (comme par exemple de dire s’il s’agit d’un objet naturel ou artificiel), il sera plus rapide et se trompera moins si le mot « carotte » a été précédé (« pré-activé ») par « lapin » que s’il a été précédé par un mot qui n’a aucun rapport avec la carotte (comme par exemple « téléphone » ; Figure 8).

L’amorçage sémantique est un des piliers de l’exploration du langage. Cependant les nombreuses études comportementales réalisées depuis le début des années 70 et utilisant ce phénomène, ont apporté des résultats contradictoires concernant l’aspect temporel, ne permettant pas de trancher entre modèle sériel et parallèle (Marslen-Wilson & Tyler, 1975; Posner & Pavese, 1998; Pulvermüller, 2007). C’est l’avènement de techniques électrophysiologiques (EEG et MEG) permettant une analyse de l’activité électrique cérébrale à l’échelle de la milliseconde qui ont permis de révéler des corrélats précoces (<200 ms) de traitement syntactiques, lexicaux et sémantiques en faveur d’un modèle parallèle (Penolazzi, Hauk, & Pulvermüller, 2007; Pulvermüller, Shtyrov, & Hauk, 2009). On peut remarquer qu’un modèle parallèle de traitement de l’information s’intègre mieux avec les modèles actuels d’organisation de la mémoire sémantique décrits au chapitre précédent qu’un modèle sériel.

1.3.1 L’amorçage sémantique

Si l’accès au sens d’un mot peut être sondé grâce à l’effet d’amorçage qu’il exerce sur des représentation associées ou reliées (Figure 8), on regroupe souvent sous ce terme des phénomènes probablement en partie différents. On peut en effet distinguer deux grands types d’activation du réseau sémantique: l’activation dite « associative » et l’activation par « association conceptuelle ». L’activation associative correspond aux idées ou mots qui viennent spontanément à l’esprit d’un sujet lorsqu’il entend un mot. Si l’on demande à un groupe de sujets de donner tous les mots qui leur « passe par la tête » après avoir entendu ou lu un mot (dans l’exemple du « lapin » cela pourrait correspondre par exemple à « carotte »,

« Bugs Bunny », etc…) on trouve une certaine homogénéité des réponses à travers les sujets d'un même milieu, d'une même culture. C'est comme cela qu'on été construites les bases de données utilisables pour créer des paires de mots « associées » (Alario & Ferrand, 1998; Ferrand, 2001). Les activations conceptuelles correspondent en revanche aux activations propres à une catégorie sémantique, sur la base de similarités conceptuelles. Par exemple pour

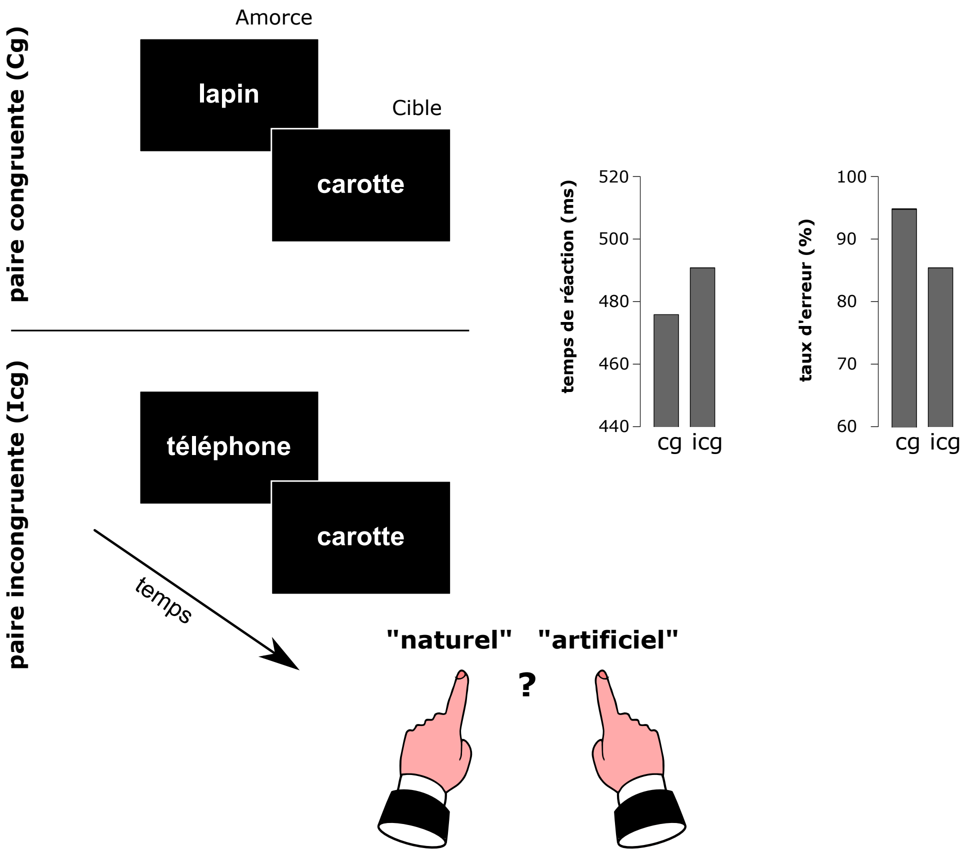

Figure 8. L'amorçage sémantique

Le sens d'un mot (ici « carotte ») est accédé plus rapidement si il est traité dans un contexte en rapport avec lui (ici « lapin »). Cette facilitation (amorçage ou priming sémantique) est mesurable au travers des temps de réponse (plus courts) et du taux d'erreurs (moindre) lors d'une tâche impliquant l'accès au sens de la cible (ici le sujet doit catégoriser la cible en « naturel » ou « artificiel »).

« lapin » ce pourrait être « hamster » ou « souris ». Cette différenciation est sous tendue par une double dissociation (partielle) des capacités d'activation sémantique observables chez certains patients atteints de démence sémantique (chez lesquels on observe essentiellement une atrophie temporale antérieure) et d'aphasie en rapport avec des lésions préfrontales ou pariéto-temporales gauches dans les suite d'un accident vasculaire cérébral (aphasie post AVC) : généralement les patients souffrant de démence sémantique ont un déficit prédominant sur l'aspect catégoriel alors que les patients souffrant d'aphasie post AVC ont un déficit prédominant sur l'aspect associatif (Jefferies & Ralph, 2006). Cependant en IRM fonctionnelle, les activations observées chez des sujet sains durant une tâche de catégorisation sémantique associative ou catégorielle révèlent dans les deux cas la mise en jeu d'un même réseau temporal antérieur / temporal supérieur et préfrontal ventral suggérant une certaine unicité du système sémantique (Jackson, Hoffman, Pobric, & Lambon Ralph, 2015). De même, il semblerait que les patients souffrant de démence sémantique et de la maladie d'Alzheimer perdent dans un premier temps leur capacité d'activation associative puis dans un deuxième temps leur capacité d'activation catégorielle (avec même au début de la maladie un aspect d'hyper-amorçage imputé à la perte des différenciations entre entités proches ; Giffard et al., 2002; Laisney et al., 2011).

Dans notre travail nous nous sommes intéressés exclusivement aux activations associatives et c'est à cela que l'on fera référence lorsque nous parlerons d'amorçage sémantique.

1.3.2 La N400 et autres marqueurs neurophysiologiques de traitement sémantique

L'électrophysiologie constitue un outil remarquable pour l'exploration fine des fonctions cognitives et en particulier pour ce qui est de leur aspect temporel. Son application à l'étude du langage a permis des avancées majeures. La technique la plus classique consiste à comparer les potentiels évoqués obtenus dans deux conditions expérimentales différentes. Un potentiel évoqué (PE) est une variation de voltage de l'électroencéphalogramme (EEG) en rapport avec un stimulus. Pour extraire ce signal du bruit de fond de l'EEG, on moyenne plusieurs dizaines (voire centaines) de segments d'EEG afin d'en augmenter le rapport signal/bruit et de ne faire ainsi ressortir que les variations de voltages liées au traitement cérébral du stimulus. En linguistique, le marqueur neurophysiologique le plus étudié est la N400, décrite pour la première fois par Kutas en 1980 (Kutas & Hillyard, 1980), Figure 9 & 10).

La N400 est un potentiel évoqué négatif survenant 400 ms après la présentation d'un mot, de topographie centro-pariétale. Elle reflète, en première approximation, la « difficulté » à accéder au sens d'un mot dans un contexte donné. Un même mot (par exemple *« piscine »*) survenant dans un contexte adéquat (par exemple « je vais aller me baigner dans la *piscine* ») évoquera ainsi une N400 de plus faible amplitude que dans une phrase qui n'a aucun rapport (par exemple « je vais aller faire des courses dans la *piscine* »). Ce phénomène serait l'équivalent en PE de la diminution du temps de réponse dans les expériences d'amorçage sémantique décrites plus haut (Figure 10). Depuis la publication princeps de Kutas, plusieurs facteurs autres que le contexte se sont révélés être capables de moduler l'amplitude de la N400. Parmi eux citons la fréquence lexicale: le sens d'un mot fréquent est « accédé » plus facilement que le sens d'un mot rare et évoque une N400 de plus faible amplitude (Kutas & Hillyard, 1980; Van Petten & Kutas, 1990; Kutas & Federmeier, 2000). A l'autre extrême, les pseudo-mots qui sont des mots prononçables, respectant les règles orthographiques mais dépourvues de sens comme par exemple « breluche », évoquent un N400 de très grande amplitude (Holcomb & Neville, 1990). L'amplitude de la N400 peut cependant parfois varier

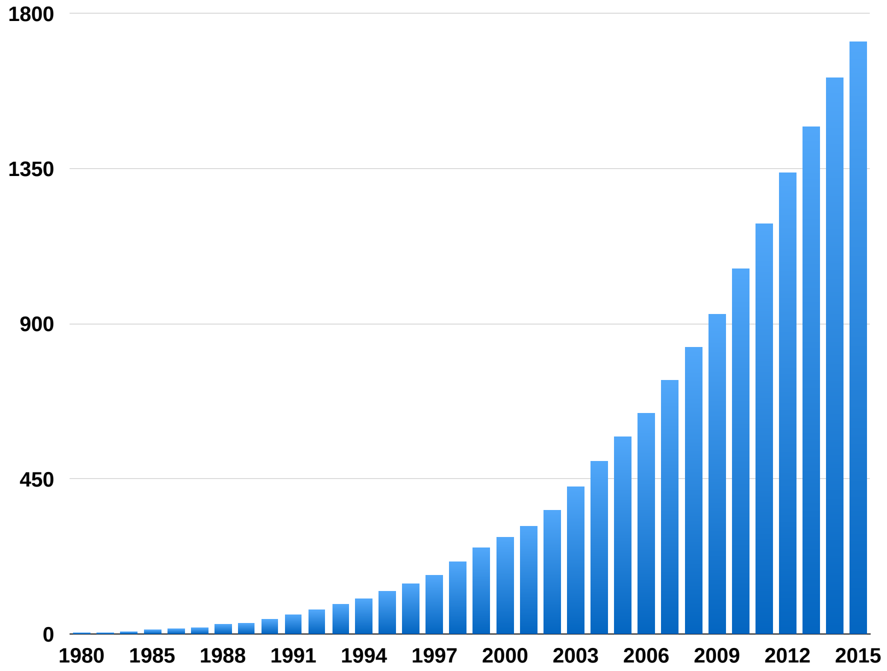

Figure 9. Références relatives à la N400 dans PubMed

Nombre total de publications référencées dans PubMed contenant l'item « N400 » cumulé depuis 1980 (date de la première publication par Kutas).

de manière contre-intuitive comme par exemple dans la comparaison entre des mots concrets et abstraits : les temps de réponse plus courts pour les mots concrets laissent supposer qu'ils sont plus facilement accédés mais pourtant leur N400 est plus ample (West & Holcomb, 2000). Une explication pourrait être la mise en jeu d'un réseau cortical plus vaste impliquant notamment les régions sensori-motrices pour les mots concrets (comme évoqué plus haut). La similitude des topographies observées indépendamment de la modalité de présentation des mots (auditive ou visuelle) suggère que la N400 est le reflet de la mise en jeu d'un réseau

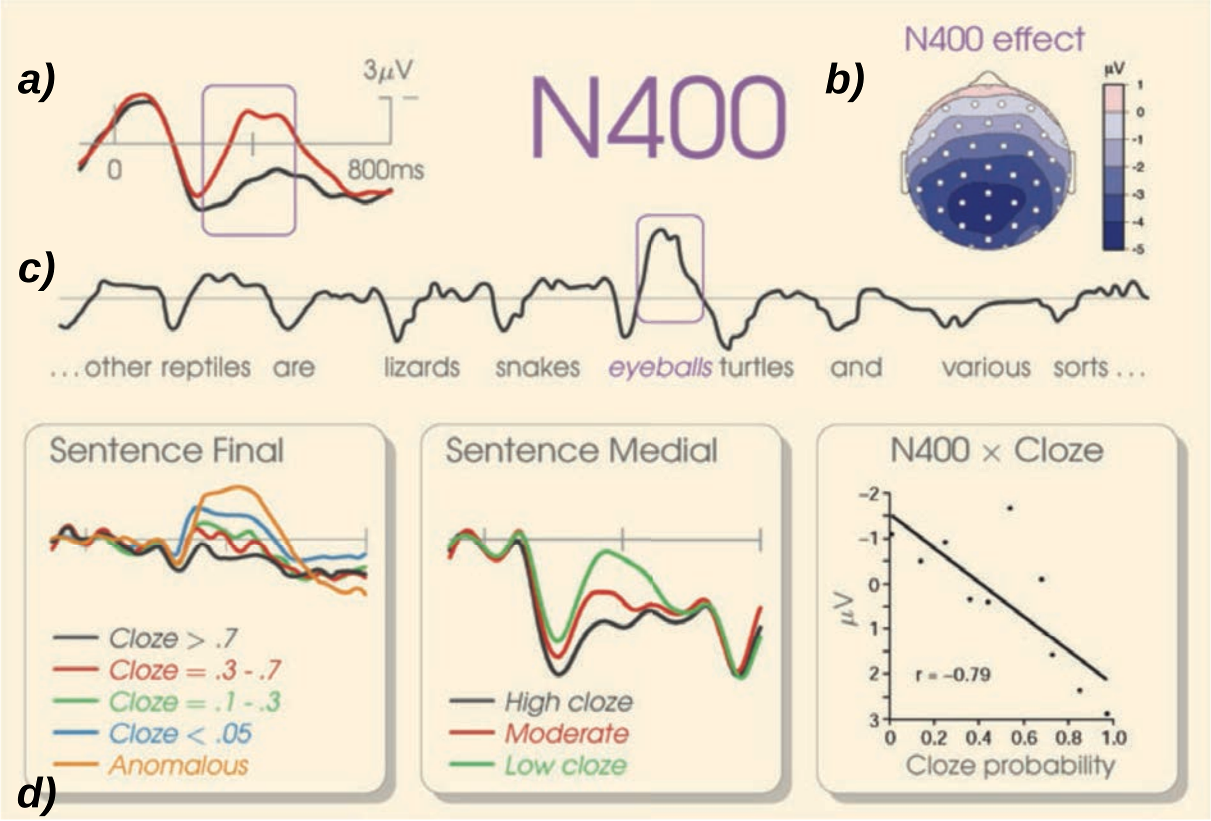

Figure 10. La N400

a) Potentiels évoqués par un mot congruent (en noir) et incongruent (en rouge) montrant la différence de voltage autour de 400 ms; b) la topographie de la soustraction (incongruent – congruent) révèle la négativité centro-pariétale typique de la N400 ; c) chaque mot évoque une N400 dont l'amplitude varie avec la difficulté à incorporer ce mot au contexte ; d) l'amplitude de la N400 d'un mot est donc inversement proportionnelle à la probabilité que ce mot survienne dans le contexte (cloze probability). Adapté de Kutas & Federmeier Annual Review of Psychology 2011).

spécifique de l’accès sémantique, comme les régions multimodales présentées dans le chapitre précédent (Domalski, Smith, & Halgren, 1991; Gomes, Ritter, Tartter, Vaughan Jr., & Rosen, 1997; Rugg & Nieto-Vegas, 1999; Hagoort & Brown, 2000). Les études réalisées en MEG suggèrent d’ailleurs que la N400 est plus le reflet d’une vague d’activité comprenant ces régions multimodales que le résultat d’un générateur fixe. Ainsi cette vague débuterait vers 250 ms au niveau de la moitié postérieure du cortex temporal supérieur gauche, puis diffuserait vers 360 ms vers les régions antérieures et ventrales du lobe temporal gauche toujours avant de se bilatéraliser vers le pôle temporal droit et les régions préfrontales. (Kutas & Federmeier, 2011). D’autres marqueurs électrophysiologiques observés dans des expériences manipulant le langage ont été décrits, certains précoces comme la ELAN (*early left anterior negativity*), d’autres plus tardifs comme la LPC (*Late Positive Component*, ou P600). Les marqueurs précoces (entre 100 et 400 ms) sont le plus souvent en rapport avec des traitements phonologiques et lexicaux. Certains travaux rapportent cependant un accès sémantique dans cette fenêtre précoce constituant ainsi un des principaux arguments en faveur du modèle parallèle (Pulvermüller et al., 2009). La signification de la LPC/P600 est quant à elle encore mal connue. Initialement décrite comme un marqueur de violation syntaxique (Friederici, 2004), elle a aussi été rapportée dans des paradigmes purement sémantiques (Hill, Strube, Roesch-Ely, & Weisbrod, 2002; Grieder et al., 2012), en condition d’inversions causales (par exemple « le chat s’est sauvé devant la souris » ; van Herten, Kolk, & Chwilla, 2005), en réponse à des métaphores (De Grauwe, Swain, Holcomb, Ditman, & Kuperberg, 2010) ou même de l’ironie (Regel, Gunter, & Friederici, 2011; Spotorno, Cheylus, Van Der Henst, & Noveck, 2013) ce qui en ferait plutôt un marqueur non spécifique de « ré-analyse » du contenu sémantique.

1.4 Résumé

Nous avons vu que la mémoire sémantique constitue la connaissance que nous avons des objets du monde. Cette connaissance est organisée en un réseau impliquant à la fois des régions sensori-motrices unimodales permettant de donner un contenu sensoriel aux représentations mentales et des régions multimodales dites associatives permettant la généralisation et l’accès à une forme plus abstraite de représentations mentales (concepts). L’accès au sens d’un mot constitue une entrée dans cette mémoire et cet accès est dépendant de facteurs externes tels que le contexte de présentation (amorçage sémantique). Cet effet du contexte est mesurable au travers du comportement (temps de réponse lors d’une tâche de catégorisation par exemple) et de réponses électrophysiologiques comme la N400 ou la LPC/P600.

Nous allons à présent introduire les connaissances actuelles relatives à la conscience et au traitement conscient de l’information, puis exposer les données disponibles sur les relations entre conscience et traitement sémantique verbal.

2 La conscience

2.1 Généralités

L’étude neuroscientifique de la conscience a connu d’importantes avancées ces 20 dernières années (Dehaene, Charles, King, & Marti, 2014; Giacino, Fins, Laureys, & Schiff, 2014). Ces progrès sont d’autant plus notables qu’ils retentissent sur la compréhension de nombreuses autres fonctions cognitives dont l’exploration est le plus souvent conduite chez des sujets conscients (mémoire, émotions, contrôle exécutif, langage, etc…). L’état conscient (forme intransitive de la conscience, *consciousness* pour les anglo-saxons) peut être défini comme un état psychologique caractérisé par la possibilité de prise de conscience subjective (forme transitive de la conscience, *awareness* pour les anglo-saxons) de contenus divers (perceptions, souvenirs, intentions, émotions, etc…). Ainsi, une représentation mentale est qualifiée de consciente si et seulement si elle est rapportable (« je suis conscient de voir ce stimulus »). L’utilisation de ce critère de « rapportabilité » est au centre des travaux expérimentaux visant à déterminer les mécanismes cérébraux de l’accès conscient. En effet certaines représentations mentales n’accèdent pas à la conscience et sont donc qualifiées d’inconscientes ou de non conscientes. A l’aide des méthodes de la psychologie expérimentale et de l’imagerie cérébrale fonctionnelle il est maintenant possible de sonder l’existence des représentations mentales conscientes et inconscientes chez des sujets sains mais également chez des patients non communicants pour lesquels les données cliniques sont parfois insuffisantes pour déterminer avec certitude leur état de conscience. Ces explorations contemporaines conjuguées à l’expertise clinique et aux techniques d’imagerie morphologique permettent de préciser le diagnostic et le pronostic de certains de ces malades. Ces nouveaux outils ouvrent de nombreuses perspectives aux conséquences médicales, éthiques, sociales et philosophiques importantes.

L’étude de la conscience étant difficilement dissociable de l’étude des patients présentant un trouble de la conscience, nous commencerons par introduire les principaux tableaux cliniques d’altération de la conscience.

2.2 Taxonomie des troubles de la conscience

Les progrès de la réanimation ont conduit depuis les années 50 à l'apparition de tableaux neurologiques nouveaux. En effet avant l'avènement de la ventilation artificielle, les patients présentant un tableau sévère d'altération de la conscience décédaient le plus souvent rapidement du fait de l'absence de protection des voies aériennes, ou moins souvent, des complications directes liées à l'agression cérébrale. Les travaux menés chez ces patients présentant un trouble de la conscience (dans le coma, en état végétatif ou en état de conscience minimale) ont eu une importance majeure dans la compréhension de la physiopathologie de la conscience. L'observation de patients a notamment révélé la distinction de deux composantes de la conscience (dans sa forme intransitive) : l'éveil (« *arousal* » en anglais) et ce que l'on pourrait traduire par le « traitement cérébral conscient » ou la conscience d'accès (forme transitive de la conscience ; « *awareness* » en anglais ; Plum & Posner, 1980). Nous reviendrons plus tard sur cette distinction importante entre conscience d'état et conscience perceptive (ou conscience d'accès).

2.2.1 Le coma

Le coma est la forme la plus sévère des troubles de la conscience, il se définit généralement par une absence d'ouverture des yeux et de motricité adaptée même en réponse à une stimulation nociceptive. Il est toujours la traduction d'une souffrance de la structure neuro-anatomique qui sous-tend l'éveil : la substance réticulée activatrice ascendante (SRAA), ses voies de projection ou ses relais thalamiques (voir Figure 11 et paragraphe 2.3.1).

2.2.2 L'état végétatif

Le terme d'état végétatif a été introduit en 1972 par Jennett & Plum, pour décrire les patients survivant à un coma qui, malgré l'absence de signe de conscience, conservent une régulation des fonctions végétatives (sous-tendues en partie par des structures situées dans le tronc cérébral) comme la ventilation, la régulation hémodynamique, les réflexes de déglutition et de toux (Jennett & Plum, 1972). Les patients en état végétatif conservent souvent une alternance de périodes d'éveil spontané et de sommeil (Bekinschtein, Golombek, Simonetta, Coleman, & Manes, 2009). Lorsqu'ils ont les yeux fermés ils sont facilement éveillables, mais l'interaction avec l'examinateur ne permet pas de mettre en évidence de comportements ou de réactions témoignant d’une quelconque perception consciente de l’environnement ou d’eux même. Seules des réactions motrices stéréotypées ou réflexes sont observables telle qu’une réaction de retrait, une grimace à la stimulation nociceptive, ou un clignement à la menace visuelle (voir tableau 1 & 2, d’après (Bernat, 2006) qui reprennent les critères publiés dans les années 90 aux USA par la *Multisociety Task Force on Persistent Vegetative* et l’ *American Neurological Association* et en Angleterre par le *Royal College of Physicians Working Group*). Notons que le terme « végétatif », qui est souvent mais incorrectement associé au terme de végétal, véhicule malheureusement une image négative des patients (« légumes ») au près des proches mais aussi des soignants. Ainsi récemment, le terme plus descriptif et aussi plus neutre de « syndrome d’éveil non répondant » (*unresponsive wakefulness syndrome ou* UWS) a été proposé (Laureys et al., 2010).

Tableau 1. Critères diagnostiques de l’état végétatif persistant (d’après Bernat, 2006)

Absence de conscience de soi ou de l’environnement
Absence d’interaction avec autrui
Absence de comportements volontaires, soutenus, reproductibles et adaptés à des stimulations visuelles, auditives, tactiles ou nociceptives
Absence d’expression ou de compréhension du langage
Cycle veille-sommeil préservé
Préservation suffisante du système nerveux autonome et des fonctions hypothalamiques pour permettre une survie à long terme avec des soins médicaux et paramédicaux adaptés
Incontinence urinaire et fécale
Préservation des réflexes du tronc cérébral (critère non indispensable)

Tableau 2. Comportements observables chez des patients en état végétatif persistant (d’après Bernat, 2006)

Cycles veille-sommeil avec alternance d’ouverture-fermeture des yeux
Respiration spontanée
Clignement des paupières ou mouvements d’errance oculaire
Nystagmus
Emission de sons mais pas de mots
Poursuite visuelle brève non soutenue
Grimaces à la douleur, expressions faciales
Bâillements, mouvements de mâchonnement
Déglutition salivaire
Mouvements incohérents des membres, posture cambrée, mouvements de décortication des membres
Retrait en flexion à la stimulation nociceptive
Mouvement de la tête et des yeux vers un son ou un mouvement
Sursaut au bruit
Myoclonies reflexes (*startle myoclonus*)
Erections liées au sommeil

2.2.3 L’état de conscience minimale

Lorsqu’un patient « émerge » de l’état végétatif mais n’est pour autant pas encore considéré comme « normalement conscient » (on verra plus loin les critères cliniques utilisables pour définir un patient « conscient ») on parle actuellement d’état de conscience minimale (ou MCS pour *Minimally Conscious State*). Ce terme sous-entend l’existence de la possibilité de traitement cérébral de type conscient. Il a été introduit en 2002 par Giacino (Giacino et al., 2002) et regroupe en réalité plusieurs tableaux neurologiques décrits antérieurement comme le mutisme akinétique ou l’état pauci-relationnel. En France on utilise encore majoritairement ce terme d’état pauci-relationnel qui a l’avantage de mettre l’accent sur l’observation clinique plutôt que sur les contenus mentaux que l’on prêtent au patient. Certains auteurs anglo-saxons préfèrent d’ailleurs le terme proche de *minimally responsive state* pour les mêmes raisons (Bernat, 2002). En plus d’avoir défini l’état de conscience minimale, Giacino a mis au point une échelle dédiée au suivi de la récupération des patients présentant un trouble de la conscience : la *Coma Recovery Scale Revised* (Giacino, Kalmar, & Whyte, 2004). Cette échelle définit les critères de sortie d’état végétatif et donc d’état de conscience minimale comme par exemple la poursuite visuelle, une réponse adaptée à la stimulation nociceptive (soustraction du stimulus) ou l’obtention de mouvements sur demande. On voit que l’idée est de mettre en exergue des comportements moteurs ne pouvant être totalement réflexes et impliquant un certain degré d’intégration consciente et de programmation intentionnelle d’une réponse motrice plus ou moins complexe à la différence de ce que l’on observe dans l’état végétatif ou le coma (voire Tableau 3 d’après Giacino, 2005). La CRS-R définit par ailleurs la sortie de l’état de conscience minimale c’est à dire l’entrée dans l’état conscient par l’obtention d’un code de communication fiable ou par l’utilisation fonctionnelle d’un objet.

La distinction entre ces différents états cliniques et particulièrement entre VS et MCS est cependant parfois difficile (Rohaut, Faugeras, & Naccache, 2013 en Annexe 5).

Tableau 3. Critères diagnostiques de l'état de conscience minimale (Giacino et al., 2002)

Au moins un des 4 comportements suivants :
1. Exécution de commandes verbales simples
2. Réponses verbales ou gestuelles « oui/non » (indépendamment de leur fiabilité)
3. Verbalisation intelligible
4. Comportements moteurs ou affectifs survenant de façon adaptée à un stimulus environnemental et non attribuables à des activités purement réflexes tel que : -Episodes de pleurs, de sourires ou de rires adaptés en réponse à un stimulus émotionnel visuel ou verbal mais pas en réponse à des stimuli neutres. -Vocalisations ou gestes qui surviennent en relation directe avec le contenu linguistique de phrases ou de questions. -Mouvements vers des objets d'allure intentionnelle. -Manipulation ou préhension d'objets de manière adaptée à leur taille et à leur forme -Poursuite oculaire ou fixation appuyée survenant en réponse directe à un stimulus mobile ou saillant.

Tableau 4. Comparaison des comportements observés chez les patients MCS, VS et comateux (d'après Giacino, 2005)

Comportement	**MCS**	**VS**	**Coma**
Ouverture des yeux	Spontanée	Spontanée	Absente
Mouvements spontanés	Automatique/Manipulation d'objets	Réflexe/Stéréotypée	Absente
Réponse à la douleur	Localisation	Stéréotypée/Retrait	Absente/Stéréotypée
Réponse visuelle	Poursuite/Reconnaissance d'objets	Fixation/Poursuite (rare)	Absente
Réponse affective	Adaptée	Aléatoire	Absente
Réponse aux commandes	Non reproductible	Absente	Absente
Verbalisation	Mots reconnaissables	Vocalisation	Absente

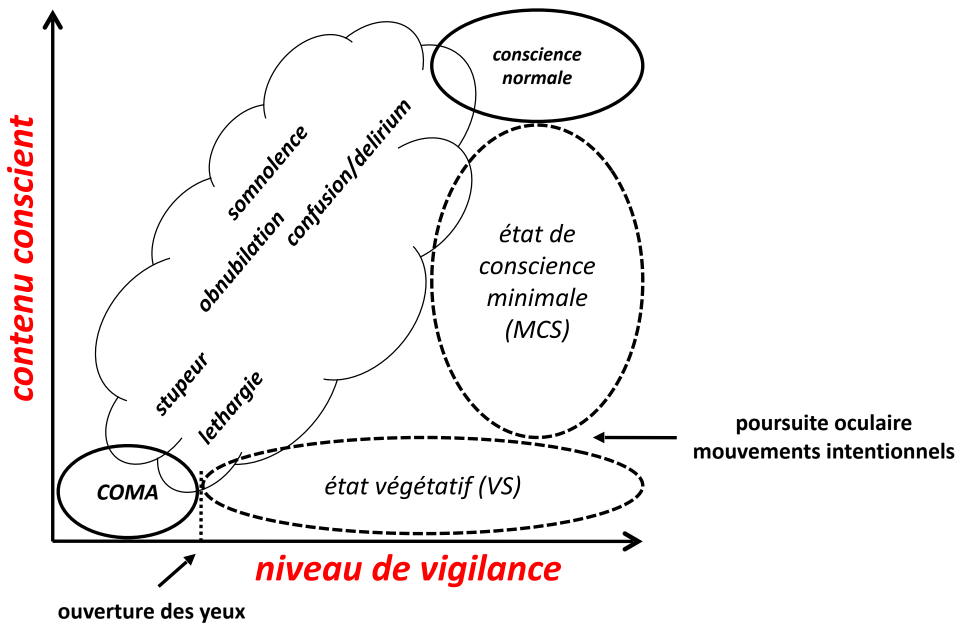

Figure 11. Représentation schématique des principaux troubles de la conscience

Les deux axes reprennent la distinction classique entre « éveil » et « contenu conscient ». Adapté de Rohaut, Kandelman, & Sharshar, 2014.

2.3 Physiopathologie de la conscience

Après avoir introduit les principaux tableaux cliniques d'état de conscience altérée, nous allons présenter les bases neurophysiologiques de la conscience. Il est classique de distinguer le système de l'éveil d'une part et un système complexe permettant le traitement conscient de représentations mentales (ou « réseau cérébral de la conscience ») d'autre part

2.3.1 Le système de l'éveil

L'éveil est sous le contrôle d'une structure cérébrale complexe le plus souvent résumée par le terme de « Substance Réticulée Activatrice Ascendante » ou SRAA. Les neurones de la SRAA ont la particularité d'exercer une action sur de vastes régions corticales et sous-corticales, régulant ainsi les différents états physiologiques que sont l'état de veille, et les différents stades de sommeil (léger, lent et paradoxal). Les noyaux constituants la SRAA sont localisés pour la plupart dans la partie postérieure de la protubérance et des pédoncules cérébraux comme en témoignent les comas observés en cas de lésions à ce niveau (Parvizi & Damasio, 2003). L'organisation anatomique de cette « substance » est extrêmement complexe (Parvizi & Damasio, 2001; Saper, Scammell, & Lu, 2005).

Les principaux noyaux de la SRAA s'organisent en deux grandes voies, directe et indirecte:

- Les noyaux pédonculo-pontins et latéral dorsal du tegmentum, cholinergiques, projetant vers les noyaux de relais thalamo-corticaux, dont l'activité est associée à une augmentation des interactions thalamo-corticales.

- Les noyaux monoaminergiques projetant directement vers le cortex cérébral regroupant les noyaux tubéro-mamillaires (histaminergiques), les noyaux du raphé dorsal et médial (sérotoninergiques), le locus coeruleus (noradrénergique) et les neurones dopaminergiques de la substance périaqueducale.

Si l'on sait depuis les travaux princeps de Magoun et Moruzzi que des lésions touchant la SRAA peuvent entrainer un trouble de la conscience avec au maximum un coma, les progrès de la réanimation ont permis d'objectiver une dissociation entre « éveil » et « conscience ». L'état végétatif en constitue la situation la plus caricaturale (Posner, Plum, & Saper, 2007) : le patient est éveillé avec parfois une préservation d'un cycle veille-sommeil (Cologan et al., 2010) mais ne manifeste aucun comportement pouvant témoigner d'une quelconque conscience. La fonctionnalité de la SRAA est donc une condition nécessaire mais non suffisante pour un état conscient.

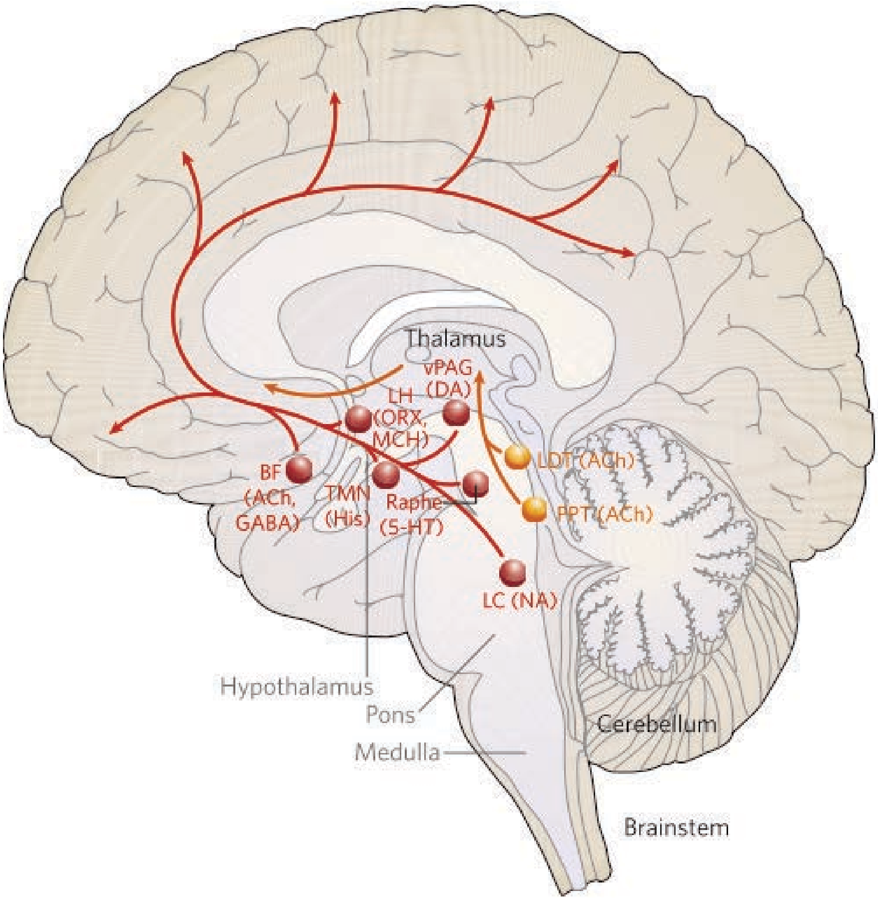

Figure 12. Principaux noyaux de la SRAA

La voie directe regroupe les noyaux monoaminergiques constitués des noyaux tubero-mammillaires (TMN) secrétant de l'histamine (His), de la substance grise périaqueducale ventrale (vPAG) sécrétant de la dopamine (DA), des noyaux du raphé médial et dorsal sécrétant de la sérotonine (5-HT) et du locus ceruleus (LC) sécrétant de la noradrénaline (NA). La voie indirecte, projetant vers les noyaux de relais thalamo-corticaux du thalamus, regroupe les noyaux cholinergiques (Ach). pédonculo-pontins (PPT) et latéral dorsal du tegmentum (LDT). Adapté de Saper et al. Nature 2005.

2.3.2 Un « réseau cérébral de la conscience »

La conscience ou, plus précisément, la capacité à traiter de l'information ou des représentations mentales de façon consciente (conscience d'accès ou conscience perceptive) requiert plusieurs éléments en plus de la fonctionnalité de la SRAA. Ces éléments sont encore l'objet de nombreuses recherches mais on peut citer :

- Un réseau thalamo-cortical traitant les informations sensorielles.

- Un réseau cérébral impliquant notamment les cortex préfrontal et pariétal, connecté aux régions sensorielles via des connexions à longue distance.

- Des capacités de modulation et d'amplification attentionnelle qui jouent un rôle dans la mobilisation active de l'information et son accès à la conscience.

2.3.2.1 Un réseau thalamo-cortical traitant les informations sensorielles

L'observation de patients cérébro-lésés révèle que pour percevoir une image, un son ou tout autre information sensorielle, le cortex sensoriel concerné doit être fonctionnel. Le système visuel est particulièrement exploré depuis la rétine jusqu'au traitement spécifique de différentes catégories d'objets (ex : visages, outils, mots, etc...) par certains réseaux corticaux spécialisés (Naccache, 2011). Un patient privé de cortex visuel primaire n'a ainsi plus de perception visuelle consciente du monde extérieur. Chez de tels patients, il est toutefois possible de découvrir des processus perceptifs inconscients et l'on parle de vision aveugle (ou *blindsight*) (Weiskrantz, 1997). Ces perceptions et processus visuo-moteurs inconscients démontrent un traitement sous-cortical de l'information à travers une voie visuelle accessoire (la voie colliculaire) qui n'est pas « branchée sur le réseau de la conscience », mais qui peut quand même influencer les comportements moteurs « à l'insu de la conscience » du patient (Poppel, Held, & Frost, 1973; De Gelder et al., 2008).

Pour autant, si l'activation de régions corticales sensorielles semble nécessaire à la perception consciente d'objets sensoriels correspondant, cette activation n'est pas suffisante. En effet l'activation de régions visuelles spécialisées (ex : aires des visages, des outils ou de la forme visuelle des mots) est possible sans perception consciente. Ce sont des expériences réalisées chez des sujets sains en condition « non consciente » qui ont permis de découvrir ce phénomène comme par exemple en utilisant des stimuli visuels « subliminaux » obtenus par masquage visuel (une cible est par exemple flashée de manière très brève et temporellement prise en sandwich par une succession de stimuli distracteurs appelés « masques » empêchant sa perception consciente). De nombreux travaux ont ainsi montré que l'activation de régions corticales correspondant à des niveaux de traitement très élaborés de l'information peuvent survenir chez un sujet conscient sans que ce dernier ne puisse y accéder consciemment (Dehaene et al., 1998, 2001; Naccache, Gaillard, et al., 2005; Dehaene & Naccache, 2006; Naccache, 2006).

La comparaison des évènements observés en condition subliminale à ceux observés en condition consciente a aussi permis de déterminer certains des corrélats qui semblent spécifiques au traitement conscient d'une information, tels que la mise en jeu d'un réseau distribué fronto-pariétal, et l'amplification au travers de boucles corticales réentrantes des aires sensorielles concernées (Figure 13).

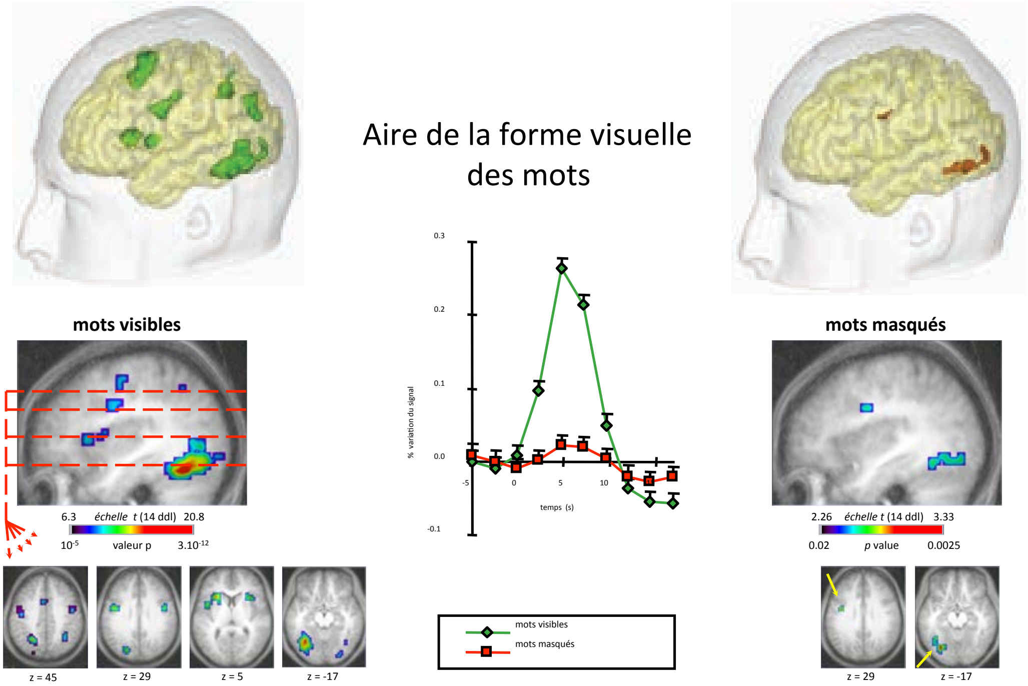

Figure 13. Différence entre traitement conscient et non conscient lors de la lecture

Activations cérébrales lors de la lecture de mots (cerveau transparent). L'aire de la forme visuelle des mots est activée par les mots masqués (à droite). En condition visible, on observe une activation plus importante de l'aire visuelle des mots et, de plus, la mise en jeu d'un réseau fronto-pariétal. Adapté de Dehaene et al. Nat Neurosci 2001.

L’activation thalamo-corticale correspondant à une modalité sensorielle est donc en fait, au même titre que la fonctionnalité de la SRAA, une condition nécessaire mais non suffisante à la conscience perceptive.

2.3.2.2 Un réseau cérébral impliquant les cortex associatifs préfrontal et temporo-pariétal connecté aux régions sensorielles via des connexions à longue distance

La comparaison des activations cérébrales obtenues en condition consciente et non consciente a permis de mettre en évidence l’implication de régions dites associatives incluant le cortex préfrontal et pariétal chez le sujet sain (Rees, Kreiman, & Koch, 2002). De même plusieurs études d’imagerie (PET-scan et IRM fonctionnelle) ont comparé l’activité cérébrale de cerveaux de sujets en état conscient, à celle de sujets inconscients : sujets endormis (Kajimura et al., 1999; Maquet et al., 2005), patients anesthésiés (Kaisti et al., 2002), patients en état végétatif (Laureys, Owen, & Schiff, 2004), patients en crise d’épilepsie généralisée ou partielle complexe (Blumenfeld, 2012). Ces études retrouvent toutes une diminution de l’activité dans le cortex préfrontal et temporo-pariétal et une diminution de la communication entre régions associatives et régions sensorielles (Figure 14), en dehors de l’épilepsie ou l’on observe une connectivité excessive.

Cette communication cohérente entre régions distantes du cortex (et notamment frontale et pariétale) semble reposer sur des activités EEG de la bande thêta, alpha et bêta (Gross et al., 2004; Gaillard et al., 2009). Une technique élégante permet d’évaluer cette communication fonctionnelle de manière passive en mesurant à l’aide de l’EEG le traitement cérébral d’une stimulation magnétique transcrânienne (TMS) délivrée au-dessus d’une région corticale donnée. Les sujets endormis ou anesthésiés ainsi que les patients en état végétatif conservent le plus souvent une réponse précoce focale à cette stimulation, mais ne présentent plus de réponse tardive, distante, maintenue et complexe (Massimini et al., 2005; Ferrarelli et al., 2010; Rosanova et al., 2012).

2.3.2.3 Des capacités d’amplification attentionnelle

En plus de l’implication des régions associatives, la comparaison des activations cérébrales obtenues en condition consciente et non consciente a révélé que l’activité au sein du cortex sensoriel était plus importante en condition consciente (Dehaene et al., 1998; Dehaene, Changeux, Naccache, Sackur, & Sergent, 2006; Naccache, 2006). L’analyse temporelle détaillée (EEG et MEG) a permis de mettre en évidence que cette hyperactivation dans la condition consciente correspondait en réalité à la sommation de deux étapes : une première étape de traitement précoce (non conscient) de l'information par les cortex primaires et secondaires spécialisés pour cette information donnée puis, une seconde étape, plus tardive dite de « réactivation » de ces mêmes régions corticales par le réseau fronto-pariétal décrit plus haut. C'est cette dernière étape qui correspondrait à la prise de conscience de l'information (Sergent, Baillet, & Dehaene, 2005). Cette seconde étape pourrait correspondre du point de vue neurophysiologique à la deuxième composante de la P300 observée en potentiels évoqués (la P3b (Karoui et al., 2014).

Les capacités de traitement conscient ne sont cependant pas illimitées et le plus souvent insuffisantes pour traiter l'ensemble des stimuli présents à un instant donné. Ainsi lorsque les ressources attentionnelles sont mobilisées, de manière endogène si le sujet focalise son attention sur un nombre restreint de stimuli ou de manière exogène si un stimulus est particulièrement saillant (comme un stimulus émotionnel par exemple), ces stimuli deviendront le plus souvent conscients au détriment des autres. Il existe plusieurs exemples, parfois ludiques, de ce phénomène d'« *inattentional blindness* » comme par exemple l'expérience du gorille qui traverse une pièce et que l'on ne voit pas consciemment du fait que notre attention est occupée à amplifier d'autres éléments de la scène visuelle (Simons & Chabris, 1999).

Sur le plan clinique, le syndrome de négligence unilatérale souvent observé dans le cadre de lésions pariétales de l'hémisphère droit correspondrait à une panne de ces processus d'amplification attentionnelle (Bartolomeo, Thiebaut de Schotten, & Chica, 2012). Chez les patients cérébrolésés en réanimation, l'examen clinique peut ainsi être rendu plus difficile en raison d'une part de ressources attentionnelles possiblement limitées et d'autre part de stimuli forts (inconfort respiratoire ou douleur par exemple) pouvant accaparer ces ressources attentionnelles limitées. La conjonction de ces deux facteurs pourrait rendre le patient plus sensible au phénomène d'« *inattentional blindness* » et conduire ainsi à une sous-estimation de son état de conscience.

2.4 Théories de la conscience

Les données exposées ci dessus ont permis d'inspirer plusieurs modèles théoriques neuroscientifiques de la conscience (voir par exemple les travaux de Tononi et Edelman, Crick et Koch, de Lamme et de Damasio). Nous présenterons ici le modèle de « l’espace de travail global conscient » (ou GNW pour *Global Neuronal Workspace*) proposé par Stanislas Dehaene, Jean-Pierre Changeux et Lionel Naccache (Dehaene & Changeux, 2011; Dehaene & Naccache, 2001). Ce modèle, qui rend notamment compte des observations empiriques présentées plus haut, a été à la base du travail réalisé durant cette thèse Il s’inspire directement de l’hypothèse formulée par le psychologue Baars, qui décrit la conscience comme l’activité d’«une collection distribuée de modules spécialisés équipés d’une mémoire de travail, société nommée « espace de travail global » dont le contenu peut être transmis à l’ensemble du système » (Baars, 1993). Dans ce modèle, à chaque instant de nombreux réseaux cérébraux modulaires traitent de l’information de manière inconsciente. Une information représentée localement au sein d’un de ces processeurs n’accéderait au contenu conscient du sujet que si et seulement si elle est mobilisée par un phénomène d’amplification attentionnelle descendante (ou *top-down*) et se propage alors, par le biais de nombreux neurones à axones longs, distribués à travers l’ensemble du cortex cérébral, pour former un état d’activité cohérente à l’échelle globale du cerveau. Cette propriété de connectivité à longue distance de ces neurones d’«espace de travail » permet, lorsqu’ils sont activés au-delà d’une certaine durée minimale, de rendre l'information amplifiée accessible à de nombreux processus mentaux tels que la catégorisation perceptive, la mémorisation à long terme, l’évaluation et l’action volontaire. Les régions associatives préfrontales et pariétales seraient particulièrement riches en neurones appartenant à cet « espace de travail global conscient » (Figure 14). Cette disponibilité globale de l’information à travers cet espace de travail neuronal global correspondrait précisément à ce dont nous faisons l’expérience sous la forme d’une conscience perceptive.

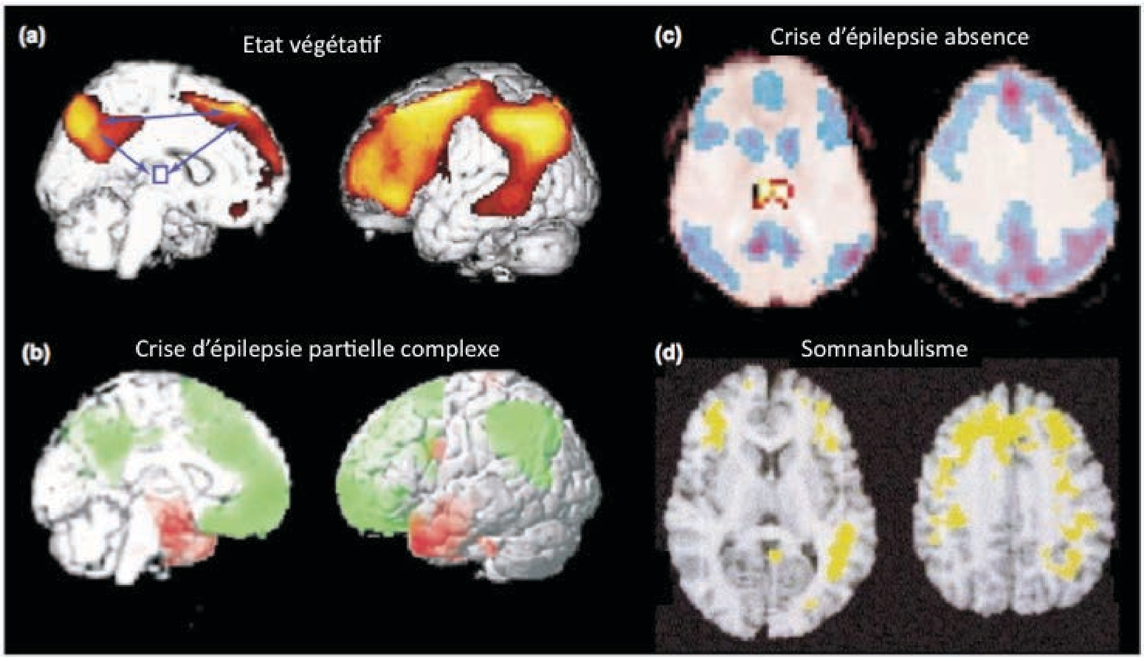

Figure 14. Le réseau fronto-pariétal de la conscience

L'étude en imagerie cérébrale fonctionnelle de divers situations cliniques associées à une perturbation sévère de l'état de conscience telle que: (a) l'état végétatif, (b) une crise comitiale de type absence, (c) une crise comitiale partielle complexe, et (d) le somnanbulisme révèlent la perturbation du fonctionnement d'un même réseau d'aires cérébrales associatives impliquant notamment les régions fronto-temporo-pariétales. Selon la théorie de l'espace de travail global, l'état conscient requiert l'existence d'une activité cohérente, complexe, et différentiée au sein de ce vaste réseau cérébral à longue distance. Adapté de Laureys, 2005.

2.5 Applications cliniques chez les patients présentant un trouble de la conscience

Une approche complémentaire à la neurologie clinique est représentée par les neurosciences cognitives de la conscience. Bien que ce problème demeure actuellement débattu, 20 ans de travaux théoriques et expérimentaux ont conduit à l'identification de propriétés psychologiques et neurophysiologiques qui semblent spécifiques au traitement conscient. De nombreux processus cognitifs peuvent survenir de façon non consciente chez des sujets conscients ou chez des patients non conscients (Dehaene et al., 2006; Laureys, 2005; Owen et al., 2005). Pourtant, trois propriétés semblent exclusivement associées au traitement conscient (Dehaene & Naccache, 2001) : (1) le maintien actif en mémoire de travail de représentations mentales ; (2) le développement de stratégies (3) le comportement intentionnel spontané. De façon similaire, alors que le traitement non conscient peut impliquer des aires corticales isolées multiples, les signatures neuronales du traitement conscient sont définies par des activations cérébrales tardives et prolongées mobilisant des réseaux thalamo-corticaux cohérents à longue distance impliquant particulièrement les régions associatives fronto-pariétales (Dehaene et al., 2006; Gaillard et al., 2009).

Sur la base de ces études, des paradigmes actifs originaux peuvent être mis au point dans le but d'améliorer notre capacité à diagnostiquer la conscience chez des patients non communicants, au-delà de l'évaluation clinique souvent prise en défaut en raison des déficits sensoriels, moteurs et cognitifs des patients (Rohaut et al., 2009, 2013). Bekinschtein et al. se sont appuyés sur la propriété de maintien actif en mémoire de travail de représentations mentales, propre à l'état conscient, et ont utilisé un paradigme de « conditionnement par trace » consistant à stimuler la cornée de patients en état végétatif (VS) à l'aide d'un souffle d'air délivré plusieurs centaines de millisecondes après la fin d'un signal avertisseur sonore conditionnel (Bekinschtein, Shalom, et al., 2009; Annexe 2). Dans une telle situation, l'anticipation du souffle d'air par le sujet nécessite de sa part l'intégration et surtout le maintien actif des stimuli en mémoire de travail, et par conséquent la prise de conscience de la relation temporelle entre le son avertisseur et le souffle d'air (Clark & Squire, 1998). La capacité à détecter cette association était révélée par l'identification d'une activité musculaire au niveau de l'orbiculaire des paupières juste avant la survenue du souffle d'air sur la cornée. De façon intéressante, les auteurs ont observé un conditionnement chez quelques patients cliniquement VS, ce qui suggère que ces patients étaient capables de conserver une information en mémoire de travail et qu'ils pouvaient donc disposer en réalité d'un certain état de conscience.

Les approches en imagerie fonctionnelle cérébrale sont également en plein essor (Coleman et al., 2009). Owen et al. ont ainsi utilisé l'IRM fonctionnelle afin de détecter la réalisation d'instructions verbales consistant à demander au patient de réaliser une tâche d'imagerie spatiale ou motrice durant des fenêtres temporelles de plusieurs dizaines de secondes (Owen et al., 2006). Utilisant plus largement cette approche chez 54 patients, ces auteurs ont pu identifier 5 patients capables de moduler de façon volontaire leur activité cérébrale. Parmi ces

5 patients, 2 étaient considérés comme VS. Chez un de ces patient en état de conscience minimale, les réponses obtenues en IRM fonctionnelle étaient utilisables pour définir un code de réponse (par exemple imaginer jouer au tennis pour signifier « oui » / imaginer visiter sa propre maison pour signifier « non »). Ce patient était ainsi capable de répondre mentalement de façon fiable et reproductible à des questions simples alors qu'il n'en était pas capable sur le plan comportemental (Monti et al., 2010).

En parallèle à de telles expériences utilisant l'IRM fonctionnelle, les paradigmes en électroencéphalographie (EEG) peuvent constituer une direction de recherche très prometteuse pour au moins deux raisons : premièrement, l'EEG présente une résolution temporelle fine permettant d'échantillonner l'activité électrique cérébrale à l'échelle de la milliseconde. Cela offre potentiellement la possibilité de suivre le flux de la conscience, et d'interagir avec le patient en temps réel. Deuxièmement, étant donné que l'EEG est une technique non invasive, avec un coût relativement faible et qu'il peut-être recueilli au lit du malade, il semble tout à fait possible de mettre au point des systèmes dédiés capables d'enregistrer de façon répétée voire continue l'activité électrique cérébrale des patients. De ce fait, l'EEG permet de suivre les fluctuations des états de conscience et de vigilance des patients VS et MCS plus facilement que l'IRM fonctionnelle. Les techniques d'EEG sont par ailleurs plus à même de permettre dans le futur l'élaboration d'interfaces cerveau-ordinateur (BCI ; Luauté, Morlet, & Mattout, 2015). Schnakers et al. ont déjà montré l'utilité des paradigmes EEG, qualifiés d' « actifs », pour explorer les réponses cérébrales volontaires à des stimuli. Ces auteurs ont pu ainsi confirmer la présence de traitements conscients chez un patient en *total locked-in syndrom* et chez des patients MCS (Schnakers et al., 2009).

Les paradigmes actifs sont importants car ils fournissent un moyen d'explorer des processus cognitifs variés en cherchant leur signature neuronale spécifique. Cependant, cette même approche confère une limitation sévère : si pour une raison ou une autre, un patient conscient ne réalise pas la tâche cognitive demandée, il devient impossible d'identifier ce sujet comme conscient. De la même façon si un sujet n'est pas éveillé durant la tâche (état confusionnel, stades de sommeil profond), ou s'il est conscient mais affecté de troubles cognitifs (aphasie, amnésie, mémoire de travail limitée ou syndrome dyséxécutif), ou encore s'il refuse de réaliser la tâche, les paradigmes actifs échouent à identifier ce sujet conscient comme effectivement conscient.

Pour toutes ces raisons, il est par conséquent utile de développer des mesures neurophysiologiques additionnelles qui peuvent échapper aux limitations des paradigmes actifs. Une voie prometteuse consiste à enregistrer l'activité électrique cérébrale en l'absence de stimulations externes. Cette approche repose sur un travail original du groupe de Raichle sur l'état cérébral de repos éveillé (ou *resting stat*e) visant à explorer les réseaux d'aires cérébrales dont l'activité est corrélée au repos (Raichle et al., 2001). L'un de ces réseaux implique les aires corticales médianes (précuneus et gyrus cingulaire postérieur) et semble lié aux processus introspectifs et à la conscience de soi. Des régions clefs de ce réseau appartiennent à un système de projection mentale général (Buckner & Carroll, 2007) qui permet à l'individu d'échapper à son « ici et maintenant », et de se projeter dans le temps (passé et futur), dans l'espace (navigation spatiale), ou dans l'esprit d'un congénère (théorie de l'esprit). Les enregistrements en IRM fonctionnelle de ces réseaux d'aires cérébrales corrélées entre elles au repos, semblent être capables de fournir des renseignements pertinents sur l'état de conscience de patients non communicants (Vanhaudenhuyse et al., 2010; Demertzi et al., 2015). Ces analyses de *resting state* ont été initiées en caméra à positons puis en IRM fonctionnelle, mais des travaux électrophysiologiques récents (He, Snyder, Zempel, Smyth, & Raichle, 2008) ouvrent la voie à des explorations plus fines de ces dynamiques d'activité en EEG. Dans un travail récent, nous avons caractérisé plusieurs marqueurs dérivés de l'EEG qui permettent de distinguer l'état de conscience minimale (MCS) de l'état végétatif (VS). Certains de ces marqueurs sont assez classiques (ex : analyse spectrale), alors que d'autres sont plus originaux (ex : complexité du signal EEG et communication fonctionnelle à longue distance). La combinaison de ces marqueurs permet également de distinguer les malades en état végétatif qui évolueront au minimum vers un état de conscience minimale, de ceux qui demeureront dans cet état (Sitt et al., 2014). Dans la même perspective, nous avons récemment élaboré un nouvel algorithme mathématique qui permet de détecter une communication cortico-corticale à longue distance et qui distingue les groupes de patients en état de conscience minimale de ceux en état végétatif (King, Sitt, et al., 2013).

Enfin, comme évoqué plus haut, une technique combinant EEG et stimulation magnétique transcrânienne (TMS) offre un accès facile à l'évaluation de la fonctionnalité de réseaux corticaux connectés à longue distance au lit du malade sans faire appel à un quelconque processus cognitif spécifique. Le principe consiste en l'exploration à l'aide de l'EEG de la dynamique spatio-temporelle corticale secondaire à une stimulation magnétique transcrânienne délivrée en regard d'une région cérébrale localisée. Il est ainsi possible d’apprécier l’intégrité du réseau d’aires associatives hétéromodales fronto-pariétales qui semble conditionner l’état de conscience. Les premières applications de cette méthode chez des sujets sains pendant le sommeil (Massimini et al., 2005), anesthésiés par midazolam (Ferrarelli et al., 2010) et chez les patients non communicants (Rosanova et al., 2012) ont apporté des résultats prometteurs. La perte de conscience ne semble pas affecter la réponse cérébrale précoce et locale en regard de la région stimulée. Inversement, la propagation plus tardive et sous une forme complexe de cette stimulation à des régions éloignées, disparaît dans tout un ensemble de situations physiologiques (sommeil lent), pathologiques (coma, VS) ou pharmacologiques (anesthésie) au cours desquelles la conscience est profondément altérée. Un index mathématique dérivé de l’analyse de ces données couplées EEG-TMS permet ainsi de quantifier l’état de conscience d’un individu (Casali et al., 2013).

2.6 Le test « local-global » de la prise de conscience

Nous allons à présent présenter un paradigme actif de potentiels évoqués cognitifs développé dans le laboratoire qui fournit un moyen très spécifique d’explorer la conscience chez des patients non communicants (Bekinschtein, Dehaene, et al., 2009).

Il s’agit d’un paradigme inspiré du classique paradigme *odd-ball* dans lequel des stimuli rares surviennent de manière aléatoire au sein d’une séquence de sons fréquents. La comparaison des PE des sons rares et fréquents révèlent chez le sujet sain deux évènements : la MMN (pour *mismatch negativity* ou négativité de discordance), puis une onde positive survenant vers 300 ms : la P300. Ce paradigme qui évalue la capacité de détection automatique de la nouveauté a été largement exploré chez les patients, notamment dans le coma, et permet de prédire un réveil dans un état meilleur que VS (Fischer et al., 1999; Fischer, Luauté, Adeleine, & Morlet, 2004; Naccache, Puybasset, Gaillard, Serve, & Willer, 2005; Luauté et al., 2005; Fischer et al., 2006; Daltrozzo, Wioland, Mutschler, & Kotchoubey, 2007; Vanhaudenhuyse, Laureys, & Perrin, 2008; Tzovara et al., 2013). Il ne s’agit pas pour autant d’un paradigme explorant les capacités de perception consciente. En effet bien que plusieurs travaux suggèrent que la P3b (deuxième composante de la P300, dissociable en P3a et P3b) soit un corrélat de traitement conscient (Dehaene & Naccache, 2001; Sergent et al., 2005), l’identification de cette deuxième composante est particulièrement difficile avec un paradigme *odd-ball* classique.

Le paradigme « Local-Global » a été spécifiquement conçu pour séparer ces deux composantes de la P300. Le patient est stimulé par des séries de sons qui sont sujettes à des variations de régularité qui peuvent se jouer soit dans une fenêtre temporelle courte intra-essai (régularité locale), soit dans une fenêtre temporelle plus longue (régularité globale à travers plusieurs essais consécutifs). Le patient reçoit la consigne de détecter et compter mentalement les violations de régularité globale. Les violations de la régularité locale conduisent à l'apparition d'une réponse précoce au sein du cortex auditif (la MMN) indépendamment de l'attention ou de la réalisation d'une tâche cognitive visuelle concomitante par le sujet. La détection de la violation de la régularité auditive globale est associée à une réponse cérébrale plus tardive, spatialement distribuée (P3b). Cette réponse n'est présente que lorsque les sujets sont conscients de la violation de la régularité globale et elle peut être détectée à l'échelle de l'individu. Les résultats obtenus à l'aide de ce paradigme chez 65 patients non communicants (24 VS, 28 MCS et 13 conscients) ont confirmé que seuls les sujets au moins minimalement conscients présentaient un « effet global ». Parmi les sujets cliniquement en état végétatif, seuls deux présentaient un effet global (Faugeras et al., 2011, 2012; Annexes 3 et 4). De façon intéressante, ces 2 patients ont montré des signes cliniques de conscience minimale respectivement 3 et 4 jours après l'enregistrement. Ceci suggère que ces 2 patients étaient sous-évalués par les échelles cliniques sous l'angle de leur niveau de conscience. La présence de cette signature EEG spécifique tardive (>300 ms), maintenue dans le temps, et qui présente une topographie de type P3b, en réponse aux violations de régularité auditive globale (effet global) permet ainsi de mettre en évidence au lit du malade une perception consciente, et donc un état conscient ou au moins minimalement conscient.

Récemment, Tzovara et al. ont cependant rapporté un « effet global » en utilisant une technique de décodage essai par essai chez des patients en coma post anoxique (Tzovara, Simonin, Oddo, Rossetti, & Lucia, 2015). Ces résultats remettent en question le caractère spécifique de la prise de conscience de cette signature. Néanmoins plusieurs limites méthodologiques peuvent expliquer ces résultats en apparence contradictoires : premièrement la mise en évidence d'un « effet global » chez certains patients présentant un EEG aréactif ou en *burst-suppression* suggère que l'effet rapporté n'est pas un corrélat de traitement conscient. Deuxièmement à l'inverse, certains patients considérés dans le coma ont possiblement été enregistrés dans un état de conscience plus riche. En effet, l'utilisation de curares est courante dans la prise en charge initiale post-arrêt cardiaque pour permettre une hypothermie thérapeutique et peut conduire à une sous estimation clinique du niveau de

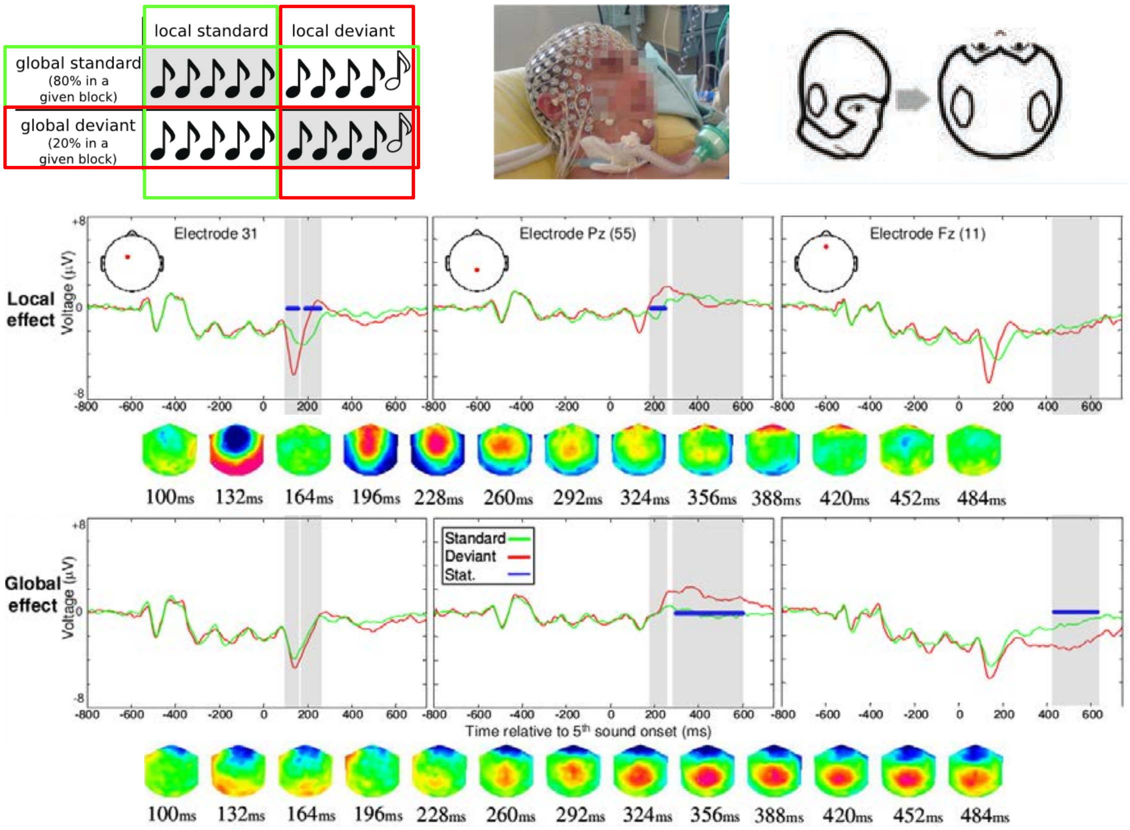

Figure 15. Paradigme « Local Global »

Le patient est stimulé par des séries de sons sujettes à des variations de régularité locale (« local deviant ») et globale (« global deviant »). Les violations de la régularité locale conduisent à l'apparition d'une réponse précoce (MMN pour mismatch negativity vers 132 ms*) suivie d'une P3a (230 ms) alors que la détection de la violation de régularité globale est associée à une P3b (260-480 ms). Cette dernière réponse n'est présente que lorsque les sujets sont conscients de la violation de la régularité globale. Adapté de Bekinschtein et al. PNAS 2009.*

conscience. Enfin la prise en compte d'effets précoces (<250 ms) pourrait en fait correspondre à une modulation du complexe MMN-P3a par le contexte global, telle que nous l'avons déjà publiée et qui ne correspond pas à la P3b, plus tardive, maintenue, corrélée à la prise de conscience de la règle abstraite définie par la variabilité inter-essais (Naccache et al., 2015).

3 Relation entre conscience et traitement sémantique verbal

3.1 Traitement sémantique non conscient chez le sujet sain

Jusqu'à la fin du XX^{ème} siècle, la question de l'existence d'un traitement sémantique de mots non consciemment perçus faisait débat. Les premiers résultats convaincants furent ceux d'Anthony Marcel. Dans ces publications princeps, Marcel montrait que des amorces masquées non consciemment perçues (il s'agissait de noms de couleur), pouvaient avoir un effet d'amorçage (sur des cibles colorées que le sujet devait identifier ; Marcel, 1983a, 1983b). Dans un deuxième travail, en reprenant les résultats de Schvaneveldt sur la polysémie[7] (caractéristique des mots ayant plusieurs sens comme par exemple le mot « avocat ») Marcel rapporta des résultats encore plus étonnants. Schvaneveldt avait montré que dans un contexte donné, une seule des représentations d'un mot polysémique était activée (« avocat » amorce « juriste » dans la séquence « médecin-avocat-juriste » mais pas dans la séquence « salade-avocat-juriste » ; Schvaneveldt, Meyer, & Becker, 1976). Marcel rapporta cependant que lorsque le mot polysémique était masqué, non seulement il persistait un effet d'amorçage (en faveur de l'existence d'un accès non conscient au sens du mot) mais qu'en plus celui-ci n'était plus restreint par le contexte (Marcel, 1980). Autrement dit Marcel avança l'idée que des représentations sémantiques pouvaient être plus riches et indépendantes du contrôle exécutif en l'absence de perception consciente.

Ces résultats passionnants ont cependant été très critiqués, pour leur faiblesse statistique, leur manque de reproductibilité (ainsi que l'accumulation d'études négatives non publiées) et enfin pour l'efficacité douteuse du masquage visuel utilisé (Purcell, Stewart, & Stanovich, 1983; Holender, 1986). Il est en effet difficile de s'assurer de l'absence de perception consciente des mots amorces en ne s'appuyant uniquement que sur le rapport subjectif du sujet. Ce n'est qu'à partir de la fin du siècle dernier et avec les expériences de Greenwald

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[7] Polysémie et homonymie sont deux types d'ambiguïtés lexicales. L'homonymie implique, à la différence de la polysémie, une différence étymologique et fait donc souvent référence à des représentations plus éloignées conceptuellement. Les publications citées utilisent souvent le terme de polysémie pour parler en réalité d'homonymie mais par souci de clarté nous utiliserons le terme polysémie.

qu'une méthode expérimentale fiable a pu être mise au point (Greenwald, Draine, & Abrams, 1996).

Pour dépasser l'écueil du rapport subjectif, Greenwald met au point une méthode d'analyse dérivée de la théorie du signal, devenue maintenant incontournable dans toute expérience utilisant des stimuli subliminaux. Cette analyse prend en compte une mesure objective de la visibilité de l'amorce masquée : le « *D-prime* » ou « *d'* ». Généralement en fin d'expérience, un bloc expérimental consiste en une tâche portant directement sur le mot masqué (par exemple une tâche de catégorisation lexicale « mot » ou « pseudo-mot »), en « choix forcé ». L'analyse des résultats se fait alors en termes de « détection des cibles » et « fausses alarmes » permettant ainsi de calculer un indice de détection (rapport signal/bruit): le « *d'* ». Un « *d'* » nul correspondant à une absence totale de détection. En corrélant l'effet d'amorçage avec cet indice de visibilité de l'amorce masquée, il devient alors possible d'estimer l'effet d'amorçage pour une visibilité nulle du mot masqué (*d'*=0), ce qui correspond à l'intercepte de la courbe de régression (voir Figure 16).

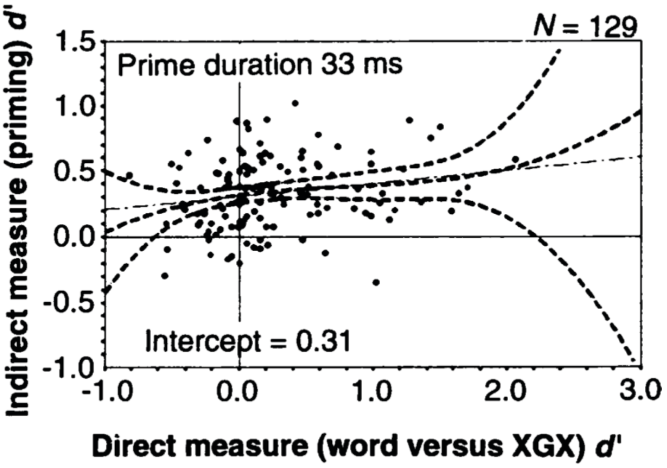

Figure 16. Exemple de courbe de corrélation entre amorçage et d'

L'effet d'amorçage sémantique est représenté en ordonnée, la visibilité de l'amorce masquée en abscisse (d'). L'intersection de la courbe de régression correspond à l'effet d'amorçage sémantique pour une visibilité nulle de l'amorce. Adapté de Greenwald et al. Science 1996.

Les résultats de Greenwald confirmeront l'existence d'un effet d'amorçage des mots masqués et poseront l'une des premières différences expérimentales entre traitement conscient et inconscient : leur évanescence. L'effet d'amorçage d'un mot masqué ne s'observerait pas au delà de 100 ms. De plus l’effet d’amorçage d’un mot masqué serait insensible au statut de l’essai précédent à la différence de la condition consciente dans laquelle la congruence de l’essai précédent module le niveau de contrôle exécutif et donc d’amorçage à l’essai suivant (« effet Gratton » ; Gratton, Coles, & Donchin, 1992).

D’autres critiques ont ensuite été avancées avec la mise en évidence de possibles effets d’apprentissage de type stimulus-réponse. Ce type d’apprentissage implicite pourrait court-circuiter le traitement sémantique de mots masqués. Ainsi dans un paradigme d’amorçage dans lequel le sujet doit catégoriser des cibles en fonction de leur valence émotionnelle (positive ou négative), le fait d’avoir catégorisé consciemment « *smut* » et « *bile* » comme négatif peut engendrer un effet d’amorçage négatif (et non positif) du mot masqué « *smile* » (Abrams & Greenwald, 2000). Un des moyens permettant de diminuer ce type de biais est de s’assurer que les mots masqués ne soient jamais présentés en condition visible (Dehaene & Naccache, 2001; Naccache, Gaillard, et al., 2005).

Moyennant un contrôle toujours plus rigoureux de ces facteurs confondants, ces effets d’amorçage sémantique de mots masqués ont été répliqués par plusieurs équipes (y compris en utilisant une technique de masquage en modalité auditive ; Daltrozzo, Signoret, Tillmann, & Perrin, 2011). De plus, ils ont été étoffés par des méthodes de neuro-imagerie mettant directement en évidence des corrélats électrophysiologiques de traitement sémantique non conscient, que ce soit dans des conditions similaires aux expériences d’amorçage précédentes (amorce masquée suivie d’une cible sémantiquement liée ou non; Deacon, Hewitt, Yang, & Nagata, 2000; Kiefer, 2002), en utilisant des nombres écrits (Dehaene et al., 1998) ou des mots à contenu émotionnel (Naccache, Gaillard, et al., 2005). Par ailleurs, il a été possible de mettre en évidence directement le corrélat électrophysiologique de traitement sémantique du mot masqué lui-même dans une expérience utilisant la technique du clignement attentionnel (*attentional blink*). Le clignement attentionnel est une autre technique de masquage visuel jouant sur la « capture attentionnelle » (deux cibles, C1 et C2, sont présentées de manière suffisamment rapprochées de telle sorte que C2 n’apparaisse pas dans le champ des représentations conscientes du sujet, encore « occupé » par C1). Cette technique a permis de révéler une modulation de la N400 du mot masqué en fonction du contexte (Luck, Vogel, & Shapiro, 1996).

Toujours chez le sujet sain, de la même manière que certains processus cognitifs telle que la détection automatique de la nouveauté auditive sont relativement préservés jusqu’aux stades de sommeil profond (Bastuji & García-Larrea, 1999), il semblerait que le traitement sémantique soit également possible en sommeil léger (Stades I et II ; Bastuji, Perrin, & Garcia-Larrea, 2002; Perrin, Bastuji, & Garcia-Larrea, 2002; Ibanez, Lopez, & Cornejo, 2006) et aussi peut-être dans une moindre mesure en sommeil lent profond (stades III et IV; Ibanez et al., 2006). Ces travaux ont par ailleurs permis de révéler une différence qualitative en termes de traitement sémantique remarquable pendant le sommeil paradoxal: les pseudo-mots (dépourvus de sens par définition) seraient traités comme des mots congruents au contexte. Ce résultat fascinant renvoie bien entendu à la relative tolérance que nous avons vis-à-vis du contenu souvent illogique de nos rêves (Bastuji et al., 2002).

3.2 Traitement sémantique chez les patients non conscients

Deux principales méthodes peuvent être utilisées pour explorer les capacités linguistiques de patients cérébro-lésés non communicants : l'IRM fonctionnelle et l'électrophysiologie

En IRM fonctionnelle, le principe consiste à contraster les activations obtenues avec des paradigmes similaires à ceux utilisés pour l'étude des réseaux sémantiques chez le sujet sain. Schiff et al. ont ainsi mis en évidence des activations corticales temporales (supérieures et moyennes) en comparant l'écoute de phrases avec ces mêmes phrases inversées (Schiff et al., 2005). Dans le prolongement de ces travaux, Davis et al. ont élaboré un paradigme hiérarchique en comparant des phrases « ambiguës » (contenant des mots polysémiques) avec des phrases non ambiguës et une condition acoustique durant laquelle un signal corrélé dépourvu de contenu verbal est présenté aux sujets [8] (Davis et al., 2007). Chez des sujets anesthésiés, des activations temporales bilatérales ont pu être mises en évidence à différents niveaux de sédation alors que des activations préfrontales et pré-motrices n'étaient présentes que pour des niveaux de sédation légère. Les phrases ambiguës entraînaient des activations supplémentaires dans les cortex préfrontal inférieur et temporal postérieur très sensibles à la sédation. Appliqué à un patient VS, ce paradigme a été capable de révéler un certain degré de préservation du traitement du langage, y compris pour les phrases ambiguës (Owen et al., 2005). Un paradigme semblable a permis de retrouver des corrélats de traitement sémantique chez 3/7 patients VS (mais pas pour les phrases ambiguës ; Coleman et al., 2007).

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[8] Le contraste avec ce « signal corrélé » est très discutable et ne permet pas d'affirmer avec certitude l'existence d'un traitement sémantique. Il pourrait en effet ne s'agir que d'un traitement lexical.

En électrophysiologie deux types de paradigmes ont été explorés. Certains travaux ont évalué la réponse au propre prénom du patient avec un paradigme *odd-ball*. Perrin et al. ont ainsi pu mettre en évidence une P300 chez des patients en état de conscience minimale (6/6) mais aussi en état végétatif (3/5) (Perrin et al., 2006). Fischer et al. ont pu confirmer ce résultat (Fischer, Dailler, & Morlet, 2008). Toutefois, le caractère très particulier du stimulus rend l’interprétation de ces résultats difficile puisqu’ils pourraient à la fois être le reflet d’un traitement sémantique, de la familiarité ou du contenu émotionnel du stimulus. Pour sonder plus spécifiquement le traitement sémantique, d’autres travaux ont tenté de répliquer chez des patients les résultats obtenus avec les paradigmes d’amorçage sémantique chez le sujet sain. A ce jour, seulement 6 études rapportant des corrélats de traitement sémantique chez des patients présentant un trouble de la conscience ont été publiées. Schoenle et al. a mis en évidence une N400 chez 12% de patient VS (Schoenle & Witzke, 2004) alors que Kotchoubey rapporte une fréquence double (20% sur 50 patients VS ; Kotchoubey, 2005; Kotchoubey, Lang, et al., 2005). Plus récemment, Steppacher et al. ont rapporté la plus grande série (53 VS et 39 MCS) et mis en évidence une N400 chez 32% des patients VS, établissant pour la première fois une corrélation entre la présence de cette N400 et le pronostic fonctionnel. Deux études rapportent une N400 chez des patients dans le coma (Kotchoubey, Daltrozzo, et al., 2005; Rämä et al., 2010). Rämä et al. soulignent le lien entre des lésions temporales et l’absence de N400. Enfin Balconi et al. n’ont pu mettre en évidence une N400 qu’à l’échelle d’un groupe de patients, sans différence entre VS et MCS (Balconi, Arangio, & Guarnerio, 2013).

Les données disponibles concernant les capacités de traitement sémantique d’une part chez les sujets conscients mais inconscients de leurs représentations et d’autre part chez les sujets ou patients non conscients, convergent donc en faveur de l’existence de représentations sémantiques inconscientes.

3.3 Hypothèses de travail

Il existe donc comme nous venons de le voir de nombreux travaux étayant l’hypothèse d’un accès non conscient au sens des mots, à la fois chez le sujet sain (expériences en condition subliminale) et chez des patients présentant un trouble de la conscience. Néanmoins les différences entre traitements sémantiques conscients et non conscients demeurent largement inconnues à ce jour.

La volonté de mieux caractériser les différences entre traitements sémantiques conscients et non conscients est à la base de ce travail de thèse. Outre son intérêt scientifique fondamental, cette caractérisation laisse entrevoir la possibilité de sonder les capacités de traitement sémantique verbale conscient et inconscient chez des patients non communicants.

Les deux grandes questions principales abordées dans ce travail de thèses sont :

1) Existe-t-il des différences comportementales, psychologiques et neurophysiologiques entre traitement sémantique conscient et non conscient ?

2) L'étude des capacités de traitement sémantique peut-elle être utile en clinique chez les patients cérébro-lésés présentant un trouble de la conscience?

Les principales hypothèses et prédictions qui ont guidé les travaux de cette thèse sont :

H1 : Un traitement sémantique est possible en l'absence de perception consciente. La prise en compte des biais évoqués partie 3 (mesure objective de la visibilité des mots masqués ; paradigme évitant l'automatisation des réponses) permet de s'assurer qu'il s'agit d'un traitement sémantique authentique.

H2 : Le modèle de traitement de l'information à deux temps, dérivé de la théorie de l'espace de travail global neuronal conscient, peut s'appliquer au traitement sémantique: un premier niveau de traitement non conscient (plus ou moins automatique cf H3) serait suivi d'un second niveau de traitement conscient sensible au contexte (influences *top-down* liées au contexte de présentation du stimulus, la posture mentale, la stratégie, etc…).

H3 : Le premier niveau de traitement sémantique non conscient peut être sensible aux influences *top-down* conscientes, et n'est donc pas automatique au sens fort du terme.

H4 : Le premier niveau de traitement sémantique non conscient est observable chez des patients présentant un trouble de la conscience.

H5 : Le deuxième niveau de traitement sémantique conscient, est observable uniquement chez des patients présentant un espace de travail global fonctionnel donc conscient ou au moins MCS.

Contributions expérimentales

1 Premier article: *Probing ERP correlates of verbal semantic processing in patients with impaired consciousness*

1.1 Présentation de l’article

Dans ce premier article, nous avons voulu adapter un paradigme d’amorçage sémantique classique dans la perspective d’une utilisation à l’échelle individuelle. Notre principal objectif était en effet la mise au point d’une méthode fiable de détection de corrélats de traitement sémantique à visée clinique. Nous avons évalué notre paradigme chez des sujets sains puis chez des patients présentant un trouble de la conscience (patients en état végétatif et de conscience minimale).

1.2 Article 1

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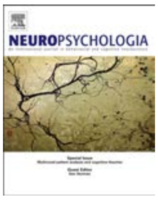

Probing ERP correlates of verbal semantic processing in patients with impaired consciousness

Benjamin Rohaut [a,d,e,f], Frédéric Faugeras [c,d,e], Nicolas Chausson [c], Jean-Rémi King [d,e], Imen El Karoui [d,e], Laurent Cohen [b,d,e,f], Lionel Naccache [b,c,d,e,f,*]

[a] AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Intensive Care Unit, Department of Neurology, Paris, France
[b] AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Neurology, Paris, France
[c] AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Neurophysiology, Paris, France
[d] INSERM, U 1127, F-75013 Paris, France
[e] Institut du Cerveau et de la Moelle épinière, ICM, PICNIC Lab, F-75013 Paris, France
[f] Sorbonne Universités, UPMC Univ Paris 06, Faculté de Médecine Pitié-Salpêtrière, Paris, France

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ABSTRACT

Our ability to identify covert cognitive abilities in non-communicating patients is of prime importance to improve diagnosis, to guide therapeutic decisions and to better predict their cognitive outcome. In the present study, we used a basic and rigorous paradigm contrasting pairs of words orthogonally. This paradigm enables the probing of semantic processing by comparing neural activity elicited by similar words delivered in various combinations. We describe the respective timing, topography and estimated cortical sources of two successive event-related potentials (ERP) components (N400 and late positive component (LPC)) using high-density EEG in conscious controls ($N=20$) and in minimally conscious (MCS; $N=15$) and vegetative states (VS; $N=15$) patients recorded at bedside. Whereas N400-like ERP components could be observed in the VS, MCS and conscious groups, only MCS and conscious groups showed a LPC response, suggesting that this late effect could be a potential specific marker of conscious semantic processing. This result is coherent with recent findings disentangling early and local non-conscious responses (e.g.: MMN in odd-ball paradigms, N400 in semantic violation paradigms) from late, distributed and conscious responses (e.g.: P3b to auditory rule violation) in controls and in patients with disorders of consciousness. However, N400 and LPC responses were not easily observed at the individual level, – even in conscious controls – , with standard ERP analyses, which is a limiting factor for its clinical use. Of potential interest, the only 3 patients presenting both significant N400 and LPC effects were MCS, and 2 of them regained consciousness and functional language abilities.

1. Introduction

The objective evaluation of cognitive abilities of non-communicating patients is one of the most challenging current medical issues. Such an evaluation is of prime importance to guide acute therapeutic decisions, to improve prognosis determination, and to inform patients' relatives. An expert, detailed and repeated clinical examination of patients, associated with the use of dedicated behavioral scales, is the best current approach. Over the last decades, new behavioral scales have been developed, aiming at detecting the emergence from comatose state (Giacino et al., 2004; Wijdicks et al., 2005), and at differentiating patients in the vegetative state from those in conscious or minimally conscious states (Fins et al., 2007). A recent assessment of these clinical and behavioral methods demonstrated that these scales importantly reduced diagnosis errors by 30–45% (Andrews et al., 1996; Schnakers et al., 2009).

While this approach remains necessary, it can only assess *overt* behaviors. In the absence of behavioral response, a second and complementary approach should thus aim at detecting *covert* cognitive abilities directly from patient's brain activity. For instance, Owen and colleagues elaborated a mental imagery task during which the patient is instructed to imagine playing tennis or walking in his home (Owen et al., 2006). This task, which requires the combination of verbal, working memory and mental imagery skills, is thought to require conscious processing (Naccache, 2006). A few clinically VS patients showed this same pattern of activation, which may be considered as an evidence for covert conscious processing (Monti et al., 2010). Following a parallel approach, we

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[*] Corresponding author at: Hôpital de la Salpêtriere, Fédération de Neurophysiologie Clinique, 47 Boulevard de l'Hôpital, 75013 Paris, France. Tel.: +33 1 42 16 22 26, mobile: +33 6 22 66 75 26.
E-mail address: lionel.naccache@psl.aphp.fr (L. Naccache).

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developed an active paradigm in which patients are asked to detect violations of auditory regularities. Crucially, our test enables us to disentangle early automatic brain responses to violations of short-range within-trials regularities (e.g. mismatch negativity, or MMN) which occur even in unconscious patients (Fischer et al., , 2004; Kane et al., 1996; Naccache et al., 2005b), from late strategic responses to violations of long-range between-trial rules (P3b response) (Bekinschtein et al., 2009). In conscious controls, the latter response requires conscious access to the between-trial rule. In patients, the occurrence of this late response was remarkably specific to clinically conscious or minimally conscious patients, as opposed to patients in VS (Faugeras et al., 2012). Indeed, similarly to the studies of Owen and colleagues, we identified two clinically VS patients who showed this response to violations of the long-range auditory rule (Faugeras et al., 2011). These two patients improved to a MCS a few days after the recordings, suggesting that we had captured signs of covert conscious processing in advance of clinical observation. We used multivariate pattern analysis techniques to improve the sensitivity of our test (King et al., 2013). However, all those tests still lack sensitivity, as evidenced by the many patients who are clinically conscious but nevertheless fail to show fMRI or EEG indices of conscious processing. The reasons for such poor sensitivity include fluctuations of vigilance, which are usual in such patients, as well as associated cognitive impairments. For instance, language impairments would impede comprehension of task instructions, whereas working memory deficits would prevent the active maintenance of the task set.

Therefore, an ideal goal would be to probe each of the patients' major cognitive modules, yielding a full neuropsychological profile, as is usual in communicating patients.

1.1. Scalp ERP signatures of verbal semantic processing: a two-stage model hypothesis

In the present work, we were interested in elaborating an ERP test probing verbal semantic processing. In 1980, Kutas and colleagues first discovered the N400, a scalp ERP event indexing violations of semantic congruity in visual or auditory sentences (Kutas and Hillyard, 1980). Since then, a rich literature investigated the precise psychological and neural properties of the N400 and of other correlates of semantic processing such as the early left anterior negativity (ELAN), or the late positive complex (LPC, also described as P600) (Kutas and Federmeier, 2011; Pulvermüler et al., 2009). The detailed description of this literature is clearly out of the scope of this experimental article, but it is noteworthy to mention the absence of consensual theoretical interpretation of the functional significance of each of these markers. While some theorists proposed to link the N400 with a late post-recognition stage of word processing (Brown and Hagoort, 1993), other models postulated that it reflects an early stage occurring prior to word recognition and semantic access (Deacon et al., 2004). In the current study we aimed at testing another model inspired by our previous works on conscious access and unconscious processing (Bekinschtein et al., 2009; Dehaene et al., 2006; Dehaene and Naccache, 2001; Gaillard et al., 2009). We previously showed, both in the visual and auditory modalities, that stimulus perception could be described as a two-stage model. While the first stage occurs in the absence of conscious access, and mostly engage stimulus processing in specialized perceptual networks, the second and later stage of processing is specifically associated with conscious access. This late stage would correspond to the broadcasting of the initial representation to a brain-scale distributed “global workspace” network (Baars, 1993; Bekinschtein et al., 2009; Dehaene et al., 2006). We and others, previously showed how this model can capture many empirical behavioral and functional neuro-imaging findings using various paradigms (e.g.: visual masking; attentional blink; neglect; distraction) and various brain-imaging tools (fMRI, high-density scal ERPs, stereo-electro-encephalography (SEEG), magneto-encephalography (MEG)) both in normal subjects and in neurological (e.g.: vegetative stage or minimally conscious patients (Bekinschtein et al., 2009; Faugeras et al., 2011, 2012; King et al., 2013); neglect patients (Sackur et al., 2008) and schizophrenic patients patients (Dehaene et al., 2003; Del Cul et al., 2006). Irrespectively of the specific stimulus attribute under consideration, the first stage would correspond to an early negativity (e.g.: N100, N200, MMN, N400), while the second and later stage of processing would be linked to a late P3b positive complex (Sergent et al., 2005; Van Gaal et al., 2014). Applied to the issue of word semantics, our theoretical approach proposes that semantic processing of words should follow the same two-stage model. The N400 would index the first non-conscious stage of semantic processing, whereas a late P3b-like complex would be the neural signature of conscious semantic processing. Indeed, several studies demonstrated that semantic processing of visual words can occur unconsciously in conscious subjects. For instance, when using a rapid-serial visual presentation (RSVP) task such as the ‘attentional blink’ paradigm, subjects failed to report target words, while a N400 signature of verbal semantic processing could still be observed (Luck et al., 1996). Sergent and Dehaene replicated this finding and further showed that while the N400 could occur in the absence of conscious access to the target word, a later event (P3b) was observed exclusively when subjects were conscious of this word (Sergent et al., 2005). Kiefer (2002) found a similar result using a masked semantic priming paradigm. These studies converge with those obtained in the auditory modality (see above) by finding a P3b component associated with conscious access. In one masking study, Naccache et al. even revealed a modulation of amygdala activity by the emotional valence of masked words in epileptic patients implanted with intracranial electrodes (Naccache et al., 2005a). Interestingly, while masked words elicited a single response in the amygdala, consciously perceived unmasked words elicited two successive responses, in agreement with our 2-stage model. In a recent ERP study investigating the semantic integration of multiple words in a visual masking paradigm, we showed that the N400 effects were similar for both masked and unmasked conditions, whereas the LPC/P600 effects were strongly affected by stimulus visibility (Van Gaal et al., 2014). Such qualitative differences are supporting our hypothesis that while the N400 is a marker of non-conscious semantic processing, the LPC/P600 indexes conscious semantic processing of words. Interestingly, other studies reported the presence of an N400 and the absence of P3b for unconsciously perceived words in the attentional blink paradigm (Luck et al., 1996; Sergent et al., 2005). Applying this 2-stage model of perception to word semantic attributes, we predicted that N400 could be observed both in conscious subjects (controls), and in DOC patients (MCS and VS), but that the LPC/P600 would be present exclusively in conscious subjects (conscious controls and some minimally conscious patients), but not in VS patients.

1.2. Verbal semantic processing in non-communicating patients

Several approaches have been developed to explore linguistic abilities in non-communicating patients. First, several studies explored brain responses to the patient's own name, a unique and extremely self-relevant word. Perrin et al. detected a P300 response to this self-related stimulus during sleep (Bastuji et al., 2002), but most crucially also in 6 out of 6 MCS patients and in 3 out of 5 VS patients (Perrin et al., 2006). Fischer et al. even reported this response in 21 out of 50 comatose patients (Fischer et al., 2008). Note however that cognitive processing of this single stimulus is not easily interpretable: it may well reflect semantic content, but also familiarity and emotional processes. A second approach consists in using fMRI contrasts between verbal and non-verbal auditory stimuli. Schiff and colleagues revealed activations of widely distributed cortical systems in some MCS patients in response to meaningful language compared to meaningless time-reversed stimuli (Schiff et al., 2005). Davis et al. designed a hierarchy of contrasts probing different stages of semantic processing, including the perception of ambiguous words within a contextual sentence (Davis et al., 2007). During propofol sedation, superior temporal areas were still responding to sentences versus noise. However, the additional inferior frontal and posterior temporal activations observed in conscious subjects in response to ambiguous versus non-ambiguous sentences were absent. Using a similar paradigm, the same group scanned non-communicating patients (Coleman et al., 2007; Owen et al., 2005). Two conscious patients showed preserved speech processing of both low-ambiguity and high-ambiguity stimuli. Crucially, 3 out of 7 VS patients demonstrated some evidence of preserved speech processing.

We will now focus exclusively on patients' studies conducted with ERP recordings. To date, six studies used sentences or word-pairs paradigms to record ERP correlates of semantic processing in patients suffering from disorders of consciousness. Schoenle et al. examined 120 patients with severe brain damage, classified into three diagnostic groups: patients in VS, patients in 'near vegetative state', and patients not in vegetative state (Schoenle and Witzke, 2004). While VS patients as a group were least likely to show N400, approximately 12% of VS patients showed a semantic N400 response. Kotchoubey and colleagues explored 50 patients in permanent VS and could identify a significant N400 response in about 20% of the population (Kotchoubey et al., 2005). Two studies reported N400 responses in comatose patients (Kotchoubey et al., 2005; Rämä et al., 2010). In particular, Rämä and colleagues showed that while a group of comatose patients ($n=7$) exempt from temporal lobe lesions showed a N400 response at the group-level, no N400 could be observed in a group of comatose patients suffering from temporal lobe lesions. Note that 4/6 patients with temporal lesions had a right temporal lesion. (Steppacher et al., 2013) recently reported an ERP study of semantic congruity conducted in 92 patients (53 VS and 39 MCS patients) with an additional measure of clinical outcome between 2 and 14 years after discharge from rehabilitation. They found signs of semantic processing in 32% of VS patients, and most importantly they reported a clear association between such ERP response and prognosis outcome, both in MCS and in VS patients. Note however that the use of only 5 electrodes did not allow for a distinction between the several ERP components previously described in the literature, such as N400 and LPC. Finally, Balconi et al. recorded ERPs during a semantic associative task in eighteen patients classified as VS or MCS, and in 20 controls (Balconi et al., 2013). A N400 effect was observed in the patients group, with a delayed latency in patients as compared to the controls group. Moreover, no clear difference was found at the group level between VS and MCS patients.

In the present study we assessed the presence of the two main ERP correlates of verbal semantic processing (N400 and LPC) in controls and in non-communicating patients suffering from disorders of consciousness (DOC). We tested VS and MCS patients and evaluated their outcome in terms of functional communication recovery. We also aimed at comparing results of this auditory verbal semantic task with a variant of the auditory odd-ball paradigm (the 'local–global' task) which we use routinely as a test of conscious processing (Bekinschtein et al., 2009; Faugeras et al., 2011, 2012; King et al., 2013). Finally, we designed our study so to perform not only group-level, but also individual-level analyses, in order to assess clinical value of our technique.

2. Methods

2.1. Controls

Twenty right-handed native French speakers volunteered to this study. One of them could not be recorded due to excessively high impedances. The remaining subjects (mean age=29 years ±7.3; sex ratio=6 males/13 females) had no neurological or psychiatric history, were free of any medication and had normal or corrected to normal vision. All participants gave written informed consent, and the experiment was approved by the Ethical Committee of the Kremlin-Bicêtre hospital (n. 98-25).

2.2. Patients

Patients were recorded (between 2008 and 2012) in distinct Intensive Care Units (ICUs) of the Pitié-Salpêtrière hospital (Paris, France). Only patients who underwent a first ERP evaluation probing automatic and conscious processing of the auditory environment (Bekinschtein et al., 2009; Faugeras et al., 2011, 2012; Naccache et al., 2005b) were included in the present study. Following this recording, which was prescribed by the clinicians in charge of the patients, we recorded them with the auditory verbal semantic paradigm (recording time was increased by 20 min). This experiment was approved by the local Ethical committee (Pitié-Salpêtrière hospital). At recording time, patients were free of any sedation. ERP acquisition was systematically preceded by a detailed clinical evaluation adapted to DOC patients: standard neurological examination, Glasgow coma scale (GCS), FOUR score (Wijdicks et al., 2005) and Coma Recovery Scale-Revised scorings (CRS-R) (Giacino et al., 2004). Patients' outcome was assessed using the Glasgow Outcome Scale Extended (GOS-E) (Jennett et al., 1981), and the CRS-R communication sub-score (0=no communication, 1 intentional but no functional communication, 2 functional communication), with a 12-months follow-up. Positive outcomes were defined by recovery of a functional communication (which also implied being conscious, and not VS or MCS).

2.3. Auditory stimulation paradigms

We designed a simple semantic priming paradigm appropriate for patients with potentially severe cognitive impairments. Each trial consisted in the presentation of a pair of semantically related or unrelated auditory words. The first (prime) word acted as a semantic inductor for the second (target) word. From a French corpus of free word association (Alario and Ferrand, 1998; Ferrand, 2001), we extracted 68 pairs of associated words. Mean free word association rate for congruent pairs was 50% (see Table 1 and Tables S1 and S2 and auditory stimuli in SOM for details). In order to exclude any confound of the congruent/incongruent factor of interest with specific words, those 68 congruent pairs were spliced to construct 68 incongruent word-pairs. For instance, the congruent pairs "*sled-snow*" and "*hive-bee*" were spliced to build two incongruent pairs "*sled-bee*" and "*hive-snow*". Crucially, given that the very same elementary words were used across congruent and incongruent, the comparison of congruent and incongruent ERPs is exclusively dependent on the semantic priming effect (see Fig. 1 and Supplementary material). Stimuli were presented through earphones (Sennheiser HD 429), using Eprime v1.1 (Psychology Software Tools Inc., Pittsburgh, PA), in a quiet room for healthy volunteers, and in the intensive care bed for patients. All subjects, – including patients – , were instructed to passively listen to pairs of spoken words and to take some precautions to limit ocular artefacts ("keep your eyes closed and try to avoid any movement"). For patients who often kept their eyes open, an eye-cover was used in order to tend to equalize photic stimulation across blocks and across patients.

In every trial, first word (prime) duration was set to 467 ms, and was then followed 400 ms later by the second word (duration ranging from 173 ms to 585 ms), corresponding to a word1–word2 stimulus onset asynchrony of 867 ms. We equated stimulus duration to 467 ms for each first word in order to keep a constant intra-trial SOA between first and second words onsets across all pairs and trials. Note that all first words had a final uniqueness point. Therefore, both acoustic and semantic onsets were time-locked across trials. The words were all intelligible (stimuli are available as SOM). Inter-trial interval randomly varied from 2300 to 2800 ms with steps of 100 ms. Each block contained the randomly delivered 136 words pairs. Controls and patients have been exposed to 2–4 blocks, depending on recording impedance conditions (cut-off < 100 kΩ) and online artefacts, in order to tend to obtain a reasonable number of EEG valid trials. As previously mentioned, all patients were also recorded under the active counting version of the 'local–global' paradigm which captures early cortical auditory responses (P1), as well as MMN and late P3 complex (Bekinschtein et al., 2009). During this first ERP session, stimuli consisted of four similar sounds (1000 or 2000 Hz with duration of 50 ms) followed by either an identical (local standard trial) or a different fifth sound (local deviant trial). Inter-stimuli interval was 100 ms (for a detailed description see (Bekinschtein et al., 2009). In conscious controls, local regularity violation (local-deviant minus local standard trials) elicits a mismatch negativity (MMN) response often followed by a transient P3a

Table 1
Lexical characteristics of primes and targets.

Lexical characteristics	Primes ($n=68$)	Targets ($n=68$)
Grammatical category (verb/name/adverb/adjective)	0/57/0/11	2/53/1/12
Concreteness (%)	47.05	38.23
Gender (masculine/feminine/neuter)	14/49/5	35/26/7
Number (singular/plural)	67/1	60/0
Movie frequency (per million of occurrence; mean (SD))	55.85 (120.18)	141.87 (168.33)
Book frequency (per million of occurrence; mean (SD))	66.60 (140.66)	141.20 (168.32)
Homograph number (mean (SD))	1.34 (0.61)	1.62 (0.71)
Homophone number (mean (SD))	3.31 (1.96)	5.16 (3.78)
Letter number (mean (SD))	6.22 (1.57)	5.00 (1.21)
Syllable number (mean (SD))	1.72 (0.61)	1.46 (0.58)
Phoneme number (mean (SD))	4.34 (1.27)	3.74 (1.17)
Orthographic uniqueness point (mean (SD))	5.71 (1.60)	4.90 (1.19)
Phonological uniqueness point (mean (SD))	4.19 (1.19)	3.74 (1.17)
Orthographic neighbors (mean (SD))	2.78 (3.51)	5.57 (4.95)
Phonological neighbors (mean (SD))	7.88 (7.62)	12.50 (8.34)
Orthographic neighborhood[a] (mean (SD))	1.90 (0.44)	1.58 (0.32)
Phonological neighborhood[a] (mean (SD))	1.51 (0.43)	1.30 (0.33)

Adapted from Matos et al. (2001).

[a] Levenshtein's distance; SD=standard deviation.

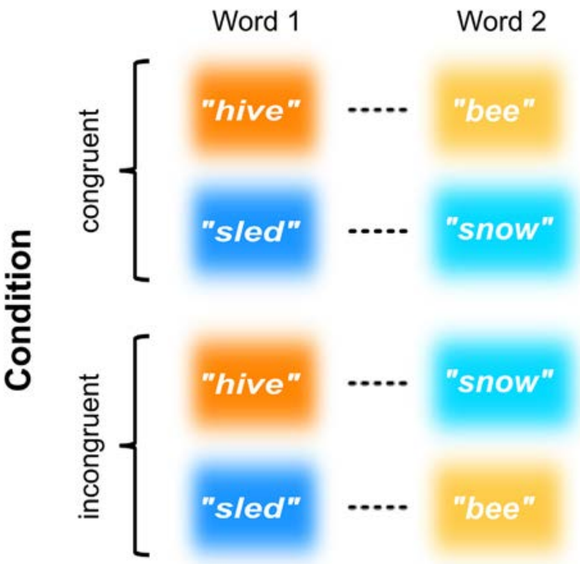

Fig. 1. Experimental design & usual N400 effect. On each trial, 2 words were sequentially presented with a fixed stimulus onset asynchrony of 867 ms. Word-pairs were either semantically congruent (e.g. *"hive-bee"*) or incongruent (e.g. *"hive-snow"*).

component (both responses are regrouped under the generic term of "local effect"). In addition to this intra-trial regularity effect, an inter-trial auditory rule was defined at the beginning of each block by the repetition of the same trials (e.g. local deviant or local standard). Patients were verbally instructed to pay attention to this structure, and to mentally count all violations of it. In conscious subjects and conscious patients, the detection of this rule violation (global-deviant trials minus global-standard trials) elicits a P3b-like potential which we called the 'global effect', which provides a very specific signature of conscious processing (Bekinschtein et al., 2009; Faugeras et al., 2011, 2012).

2.4. EEG recording and processing

EEG was sampled at 250 Hz with a 256-electrode geodesic sensor net connected to a high impendence amplifier (EGI, Oregon, USA) referenced to the vertex. Impedances were controlled inferior to 100 kΩ. Data were filtered from 0.5 Hz to 20 Hz. For the semantic paradigm, trials were segmented from −200 ms to 1000 ms relative to the onset of the second word. For the 'local–global' paradigm, trials were segmented from −200 ms to +1300 ms relative to the onset of the first of the five sounds.

Trials with voltage exceeding ±100 μV or electro-oculogram activity exceeding ±70 μV, or containing eye-blinks were rejected. Trials with more than 10/256 bad channels were rejected. For the remaining trials, bad channels were interpolated from contiguous electrodes. Remaining trials were averaged in synchrony with respective stimulus onset, digitally transformed to an average reference, and corrected for baseline over a 200 ms window before stimulus onset for the semantic paradigm, and over an 800 ms window for the 'local–global' paradigm. All pre-processing stages were performed in the EGI Waveform Tools Pack. Voltage topographical maps were plotted with Cartool software programmed by Denis Brunet (http://brainmapping.unige.ch/Cartool.htm).

Cortical current source density mapping was obtained using a distributed model consisting of 10,000 current dipoles. Dipole locations and orientations were constrained to the cortical mantle of a generic brain model built from the standard brain of the Montreal Neurological Institute using the BrainSuite software package. This head model was then warped to the standard geometry of the sensor net. The warping procedure and all subsequent source analysis were processed with the BrainStorm software package (http://neurimage.usc.edu/brainstorm). EEG forward modeling was computed with an extension to EEG of the overlapping-spheres analytical model. Cortical current maps were computed from the EEG time series using a linear inverse estimator (weighted minimum-norm current estimate or WMNE, see (Tadel et al., 2011) for review). We computed sources of the grand-average calculated in controls (incongruent pairs minus congruent pairs). Source estimations were converted in *Z*-score in comparison with a 200 ms long baseline window preceding the onset of the second word.

2.5. Statistical analyses

We used the same method as previously reported in our previous publications on the 'local–global' paradigm (Bekinschtein et al., 2009; Faugeras et al., 2011, 2012).

Group analyses were computed using sample-by-sample paired *t*-tests with a triple criterion: *t*-test *p* value was categorized in three levels (non-significant, $0.01 \le p < 0.05$ or $p < 0.01$), for a minimal duration of 10 consecutive samples (40 ms) at least on 10 electrodes.

A region of interest (ROI) approach was also used by computing sample-by-sample paired t-tests on the mean signal averaged across 10 contiguous electrodes centered on the spatial maximum of the effect in the controls group. Peaks of the ERP effects were calculated as the maximal difference between incongruent and congruent averaged ROIs ERPs. Note that this method is circular when evaluating statistical significance of an ERP effect when applied to the controls group due to a "double-dipping" issue (Kriegeskorte et al., 2009), but is valid when exploring patients' groups, and individual-subject data.

In order to take advantage of the high-spatial resolution we supplemented the electrode-by-electrode and ROI analyses with a multiple-linear spatial regression approach able to exploit scalp topographies of voltages (Pegado et al., 2010). N400 and LPC effect were defined by a 257-values vector corresponding to the averaging of voltages during the relevant time-window in controls subjects (436–516 ms for N400; 652–1000 ms for LPC, see Fig. 2b). Then for each patient group (DOC, VS and MCS subgroups) voltage time series were regressed with a model including the effects of interest and a constant regressor. For each group of patients, distributions

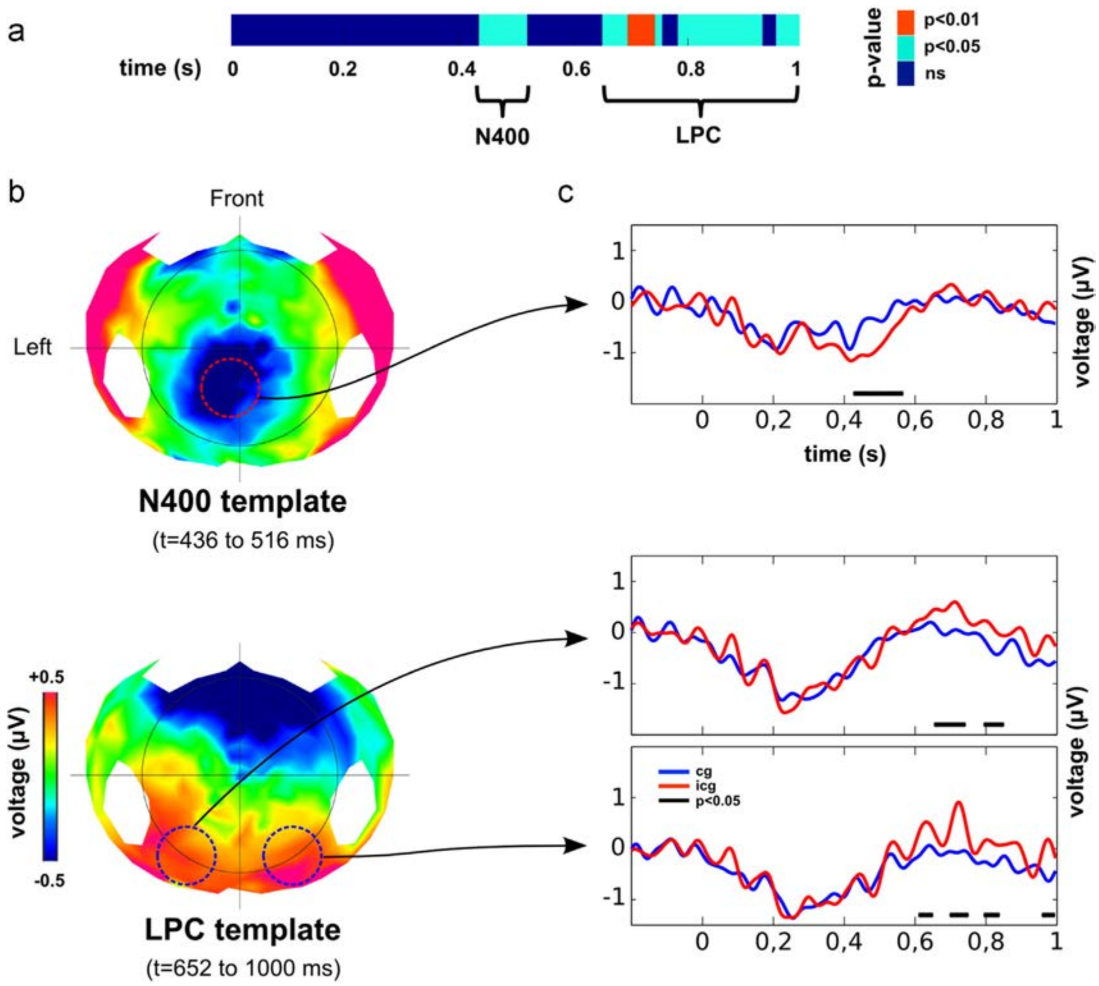

Fig. 2. N400 and LPC in controls (a) overview of semantic congruity effects in the controls group using the triple threshold paired t-tests approach (see section Methods). Two significant periods were found, corresponding respectively to the N400 and to the LPC. (b) N400 and LPC templates defined in this controls group and used for linear regression on patients' group and individual data. These voltage topographies were calculated by the subtraction (incongruent–congruent) in the N400 and LPC time windows. (c) ERPs for incongruent and congruent conditions computed in 3 regions of interest (note that this result is circular, and is only shown for a descriptive purpose in the perspective of patients' data analysis).

of coefficients of interest were tested against the null hypothesis with an unpaired t-test ($p < 0.05$ which correspond to a t-value > 1.96).

Individuals' statistics were computed using a sample-by-sample unpaired t-test between experimental conditions across trials with a triple criterion: $p \leq 0.05$ on a minimum of 5 consecutive samples (20 ms) and on a minimum of 10 electrodes. In order to further assess the power of observed effects, we categorized the significance of the semantic effect for each time-sample using a 6-level p-value scale: ≤ 0.05, ≤ 0.01, ≤ 0.005, ≤ 0.001, ≤ 0.0005 and ≤ 0.0001. A last correction was then used on each recording in order to increase the specificity of our analyses. On the basis of the group analysis, we categorized a semantic congruity effect as a N400 if its onset ranged from 200 to 600 ms after the onset of the second word, and as a LPC if its latency ranged from 600 to 1000 ms. All p-values of interest (200–1000 ms after the onset of the second word) superior to the lowest p-values observed in this recording within the baseline time-window and the first 200 ms (-200 to $+200$ ms) were discarded. Finally, when p-values of interest were equal to this minimal p-value, the effect was considered significant only if its duration exceeded the longest duration observed at this p-value level within the baseline time-window. All statistics analyses were computed using Matlab 7.0 (Natick, MA, USA).

Individual regression analyses were computed with a similar method as in the group analysis. However, to perform a trial per trial statistic, we regressed each trial (congruent or incongruent) to the N400 and LPC templates. To avoid circular analysis for controls, templates were individually recomputed from the data of the 18 other subjects (e.g. "$n-1$ method"). We then compared, trial per trial, the beta values of congruent and incongruent trials using an unpaired t-test (see Fig. 4).

3. Results

We will first present group-level results both in controls and in DOC patients and then turn to individual statistics. Finally, diagnosis and outcome values of ERP effects will be reported for DOC patients.

3.1. Group-level analyses

3.1.1. Control subjects

The first significant ERP difference between incongruent and congruent trials was a N400 response lasting from 436 ms to 516 ms after the onset of second word (peaking at 472 ms, see Fig. 2). This N400 response was followed by a late and sustained posterior positive complex spanning from 652 ms to 1000 ms after the onset of the second word (peaking at 728 ms). This response shows the properties of the late positive complex (LPC) or P600 associated with the occurrence of semantic or syntactic incongruity (Pulvermüller et al., 2009).

We then estimated the cortical sources of these 2 ERP effects. The N400 effect was associated with an increase of cortical currents in the right temporal pole, in bilateral fronto-polar cortices with a right predominance, and left DLPFC (middle frontal gyrus), whereas the LPC corresponded to cortical activations maximum within left DLPFC (inferior frontal gyrus) and right fusiform gyrus (see Fig. 4).

3.1.2. *DOC patients*

We recorded 30 DOC patients (15 VS 15 MCS). One (MCS) patient has been excluded because of too many eye-blink artefacts. Fifteen patients were in vegetative state (VS), and fourteen were in the minimally conscious state (MCS) (see Table 2). We report the results of the DOC group as a whole, as well as results of the VS and MCS subgroups.

3.1.2.1. N400. The triple-threshold analysis revealed a significant effect within the N400 window in each of the 3 groups, spanning respectively from 280 to 394 ms for the DOC group, from 184 to 364 ms in the VS subgroup (peaking at 348 ms), and from 316 to 472 ms in the MCS subgroup (peaking at 360 ms).

Visual inspection of scalp topographies and the regression analysis to controls N400 template showed a partially preserved topography in the DOC group (marginally significant but long-lasting values in the regression statistics). Comparisons of the topographies of the VS and MCS subgroups with controls did not reveal any significant resemblance. Finally, we noted that the N400 occurred at a shorter latency than in controls (280–314 ms in DOC patients versus 436–516 ms in controls). No N400 effect was found when using the ROI approach. The N400 was more posterior in VS patients than in controls, and presented a right lateralization in MCS patients (see Fig. 3).

3.1.2.2. LPC. None of the three methods revealed any effect in the LPC window neither in DOC patients nor in VS patients. In sharp contrast, a strong LPC effect was observed in the MCS subgroup. Note that this effect had all the expected properties of the LPC: (1) it extended from 732 to 804 ms (peaking at 744 ms), a period included in the span of controls' LPC, (2) it showed a typical LPC topography both on visual inspection and with the regression analysis, and (3) it was significant in the left posterior ROI defined in controls, and close to significance in the right posterior ROI (see Fig. 3).

3.2. *Individual-level analyses:*

3.2.1. *Controls*

We probed effects of semantic congruence in individual subjects by looking for significant differences in the N400 and LPC windows using the usual triple-threshold, and also by running regression analyses to detect effects with expected topographies. A significant N400 effect was observed in 8/19 subjects (42.1%) with triple-threshold approach, and in 8/19 subjects (42.1%) with the regression analysis. Note that 5 subjects were positive with the two methods (see Fig. 5). We found a significant LPC in 6/19 subjects (31.6%; triple-threshold approach), and in 8/19 subjects (42.1%; regression approach). Three subjects were positive with the two methods. When requiring the presence of at least one of these two effects (N400 and/or LPC, using the triple-threshold approach), we were able to detect correlates of word-pair semantic processing in 11/19 (57.8%) of subjects. Note that we observed a large variability in latencies for both the N400 and the LPC (N400: 480[± 63] ms; LPC: 853[± 92]). There was also a large variability in topography: only 5 out of the 8 significant N400 as identified with the triple-threshold criteria had a significant N400 topography with the regression approach, and similarly only 3 out of the 6 LPC had a significant LPC topography.

3.2.2. *Patients*

A N400 effect was found in 6/29 DOC patients (5/14 MCS; 1/15 VS) with the triple-threshold approach. No additional patient could be identified using the regression approach (see Fig. 5). Therefore, the N400 component tended to be more present in MCS than in VS patients ($\chi^2=3.7$; $p=0.05$).

A LPC response was observed in 6 DOC patients (5/14 MCS; 1/15 VS) with the triple-threshold approach, and 3 additional MCS patients were positive using the regression approach. Overall, 8 MCS patients showed a LPC as compared with a single VS patient. The LPC was thus significantly more frequent in MCS than in VS patients ($\chi^2=8.6$; $p=0.003$). Three MCS patients showed both a N400 and a LPC response.

Given the variable number of blocks and of trials across patients and controls, we checked for the absence of relation between the presence/absence of N400 or LPC and the number of valid trials kept for EEG analysis after artefact rejection. For N400, observed values were of 285 ± 45 trials for 'N400+' and 256 ± 66 for 'N400−' in controls (*t*-test *p*-value=0.14), and of 304 ± 49 trials for 'N400+' and 293 ± 98 for 'N400−' in patients (*t*-test *p*-value=0.35). Similarly for LPC, observed values were of 261 ± 57 trials for 'LPC+' and 271 ± 61 for 'LPC−' in controls (*t*-test *p*-value=0.37), and of 278 ± 56 trials for 'LPC+' and 300 ± 97 for 'LPC−' in patients (*t*-test *p*-value=0.31).

3.2.3. *Diagnostic and prognostic power of ERP effects*

All patients were also recorded with the 'local–global' paradigm, which enables the detection of the low-level auditory P1 ERP component, of the automatic MMN response ('local effect') and of the ERP response to violations of the current auditory rule ('global effect'). As mentioned before, the latter is a very specific, – but weakly sensitive – , marker of conscious processing.

We now provide a full description of the diagnostic (being clinically diagnosed as VS or MCS) and prognostic (recovery of functional communication at 12 months, which also corresponds to being conscious and not in the vegetative or minimally conscious states) values of each of 5 ERP effects analysed in each patient: auditory P1, MMN, 'global effect', N400 and LPC. We decided to use a conservative statistical approach by considering only ERP effects passing the triple-threshold criterion (see Table 2, which also provides GOS-E outcomes). Prior to these analyses we noted that clinical diagnosis is a powerful predictor of functional communication outcome: whereas a positive outcome was observed for 7/14 (50%) MCS patients, only 1/15 (7%) VS patients recovered functional communication ($\chi^2=6.8$, $p=0.009$).

3.2.3.1. Auditory P1. Only 4/29 patients did not show early cortical P1 responses to sounds. Those 4 patients were in a VS during ERP recording (3 from anoxic lesions and 1 from severe traumatic brain injury). The absence of P1, in the absence of severe dysfunction of the peripheral or central auditory pathway was systematically associated with VS (Sensibility (Se)=100%; Specificity (Sp)=27%; Predictive Positive Value of being MCS (PPV)=56%; Negative Predictive Value of being MCS (NPV)=100%). Therefore, the P1 showed an ideal sensitivity for MCS, and its absence perfectly predicted the VS. Given this strong association with VS, analyses of the prognostic value of this ERP component is essentially confounded with the initial clinical status (Se=100%; Sp=19%; PPV=32%; NPV=100%).

3.2.3.2. *MMN (or local effect)*

19/29 patients had a significant MMN, including 12/14 MCS patients and 7/15 VS patients (Se=86%; Sp=53%; PPV=63%; NPV=80%). These values resemble to those observe for the P1 ERP component. MMN showed a similar sensitivity for prognosis and a strong NPV (Se=88%; Sp=43%; PPV=37%; NPV=90%).

3.2.3.3. N400. 6/29 patients presented a significant N400 response. All but one (5/6) were in a MCS (Se=36%; Sp=93%;

Table 2
Patients' characteristics, ERP results and outcomes.

State	Age	Sex	CRS sub-scores[a]						CRS											
			1	2	3	4	5	6	Total	Etiology	Delay (days)[b]	P1/ N1	Local Effect	Global Effect	N400	LPC	Language outcome [c]	Consciousness recovery	GOS-E 6 months	GOS-E 12 months
MCS-1	56	Male	1	3	0	1	0	1	6	Other	134	+					0		2	1
MCS-2	59	Female	2	0	3	3	1	0	9	Other	60	+					0		1	1
MCS-3	34	Male	2	3	4	1	0	2	12	TBI	26	+	+				2	+	4	6
MCS-4	33	Female	1	3	2	2	0	2	10	Stroke (c)	10	+	+				1	+	3	4
MCS-5	24	Male	1	3	2	2	0	2	10	TBI	1259	+	+				0		3	3
MCS-6	43	Female	1	3	2	1	0	2	9	Stroke	25	+	+			+	0		2	1
MCS-7	47	Male	3	3	3	2	0	1	12	TBI	1583	+	+		+		2	+	3	3
MCS-8	54	Male	2	3	2	0	0	2	9	Stroke (c & b)	60	+	+		+		0		1	1
MCS-9	64	Male	3	0	2	2	1	2	10	Stroke (b)/other	30	+	+		+	+	2	+	3	3
MCS-10	28	Male	1	3	0	1	0	1	6	TBI	17	+	+	+			2	+	4	7
MCS-11	18	Male	1	3	3	1	0	2	10	TBI	33	+	+	+			2	+	7	7
MCS-12	58	Male	3	3	2	2	1	2	13	Anoxia	60	+	+	+		+	2	+	1	1
MCS-13	23	Male	2	3	0	1	0	2	8	Other	87	+	+	+	+	+	1		3	3
MCS-14	36	Male	1	1	0	1	1	2	6	Stroke (b)	24	+	+	+	+	+	2	+	3	3
VS-1	59	Male	1	0	0	1	0	1	3	TBI	30						0		1	1
VS-2	29	Female	0	0	1	1	0	2	4	Anoxia	26						1		3	3
VS-3	78	Male	0	0	1	1	0	2	4	Anoxia	15						0		1	1
VS-4	52	Male	1	0	1	1	0	1	4	Anoxia	23						0		1	1
VS-5	22	Female	1	0	2	1	0	2	5	Anoxia	30	+					0		2	2
VS-6	48	Male	0	1	1	2	0	2	6	Stroke (c)	497	+					0		2	1
VS-7	59	Female	1	1	2	1	0	1	6	Stroke (c)	21	+			+		2	+	4	4
VS-8	46	Male	1	0	1	1	0	2	5	Anoxia	155	+					0		2	2
VS-9	31	Male	1	0	0	1	0	1	3	Anoxia	7	+	+				0		2	1
VS-10	37	Female	1	0	2	0	0	1	4	Stroke (c)	194	+	+				0		2	2
VS-11	37	Female	1	1	1	1	0	1	5	Stroke (c)	62	+	+				1		3	3
VS-12	48	Male	0	0	2	1	0	2	5	Anoxia	15	+	+				0		1	1
VS-13	40	Male	1	1	2	1	0	1	6	TBI	62	+	+				0		1	1
VS-14	62	Male	0	0	0	0	0	1	1	Other	30	+	+			+	0		1	1
VS-15	64	Female	1	1	2	1	0	2	7	Other	23	+	+				0		2	2

CRS-R=Coma Recovery Scale-Revised.

[a] CRS-R subscores incude: 1: auditory function; 2: visual function; 3: motor function; 4: oromotor/verbal function; 5: communication scale; 6: arousal scale.

[b] Delay from acute brain injury (in days); TBI=traumatic brain injury; VS=vegetative state; MCS=minimally conscious state; Etiology column: stroke could affect cortical (c), or brainstem structures (b).

[c] Language outcome=best CRS--sub-score-5 after ERPs recording. GOS-E=Glasgow Outcome Scale-Extended.

PPV=83%; NPV=61%). Thus, the N400 showed an interesting capacity to differentiate MCS from VS patients, as well as a valuable positive predictive value for the MCS. Note that the etiologies of patients showing a N400 response included stroke and TBI, but not anoxia. In terms of prognostic value, the presence of a N400 component was a specific marker of communication recovery, endowed with a strong negative predictive value (Se=50%; Sp=90%; PPV=67%; NPV=83%). Interestingly, the single VS stroke patient with a N400 response recovered consciousness and functional communication.

3.2.3.4. LPC. 6/29 patients presented a significant LPC response, only one of which suffering from anoxia. All but one (5/6) were in a MCS (Se=36%; Sp=93%; PPV=83%; NPV=61%). Among those 6 patients, 3 also showed a N400 response. Note that two of them recovered consciousness and functional communication, whereas the third remained in a MCS. In terms of prognosis, only 3 of the LPC+ patients recovered a functional communication (Se=38%; Sp=86%; PPV=50%; NPV=78%). The single VS patient with a LPC response did not recover functional communication.

3.2.3.5. Global effect. 5/29 patients presented a significant 'global effect', only one of which suffering from anoxia. All patients showing a 'global effect' were in a MCS (Se=36%; Sp=100%; PPV=100%; NPV=62%), as we previously described in a larger series (Faugeras et al., 2012). In terms of prognostic value, presence of a 'global effect' component was a specific marker of communication recovery, endowed with a strong negative predictive value (Se=50%; Sp=95%; PPV=80%; NPV=83%).

4. Discussion

In the present study we tried to develop an electrophysiological index of semantic processing which could be used to refine the diagnosis and prognosis of patients with disorders of consciousness in addition to clinical and behavioral examination. To this end, we recorded two ERP markers (N400 and LPC) elicited by pairs of semantically congruent auditory words, as compared to incongruent words. Our results are twofold: First, we provide novel findings regarding the spatio-temporal cortical dynamics of verbal semantic processing in conscious subjects. Second, we determined the medical value and shortcomings of those markers in vegetative and minimally conscious patients. Those two points will be discussed in turn.

4.1. Verbal semantic processing in conscious healthy subjects

The earliest significant difference between congruent and incongruent word pairs was the classical N400 component,

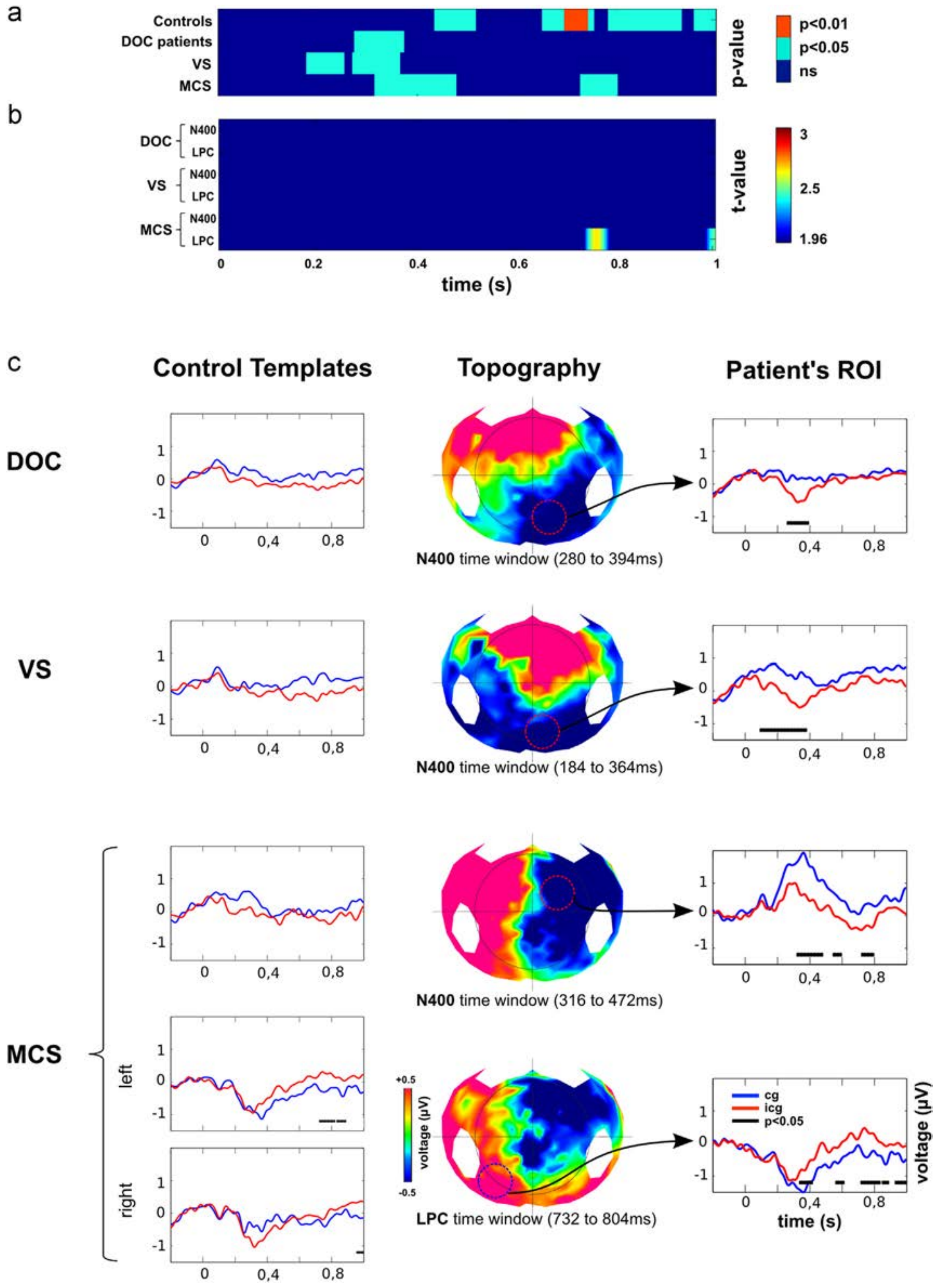

Fig. 3. N400 and LPC in DOC patients (a) overview of semantic congruity effects analysed with the triple-threshold method in: controls (upper line, see Fig. 2a), DOC patients (second line), MCS patients (3rd line) and VS patients (4th line) groups. A N400 ERP was detected in the 3 groups of patients, whereas the LPC was only found in the MCS group. (b) Overview of semantic congruity effects analysed with the regression approach using controls N400 and LPC templates in: DOC patients (1st & 2nd lines), in MCS (3rd & 4th lines) and in the VS (5th & 6th lines) groups. This analysis confirmed that the LPC detected in the MCS patients group with the triple-threshold method presented a significant normal LPC topography. (c) Patients' groups ERPs and voltage topographies in N400 and LPC ROIs defined with the controls group.

spanning from ~400 ms to ~550 ms after the onset of the second word. We did not find any earlier ERP response to semantic congruity, such as the early left anterior negativity (ELAN) (Friederici and Mecklinger, 1996). This negative finding may have several explanations. First, the ELAN may actually be a marker of early syntactic processing, whose absence is congruent with the absence of any syntactic structure in our stimuli (Friederici, 2004). Alternatively, it cannot be excluded that, due to the size of our sample, we lacked sufficient statistical power to detect this early marker.

In agreement with previous reports (Kutas and Federmeier, 2011), the N400 consisted in a centro-parietal negativity with

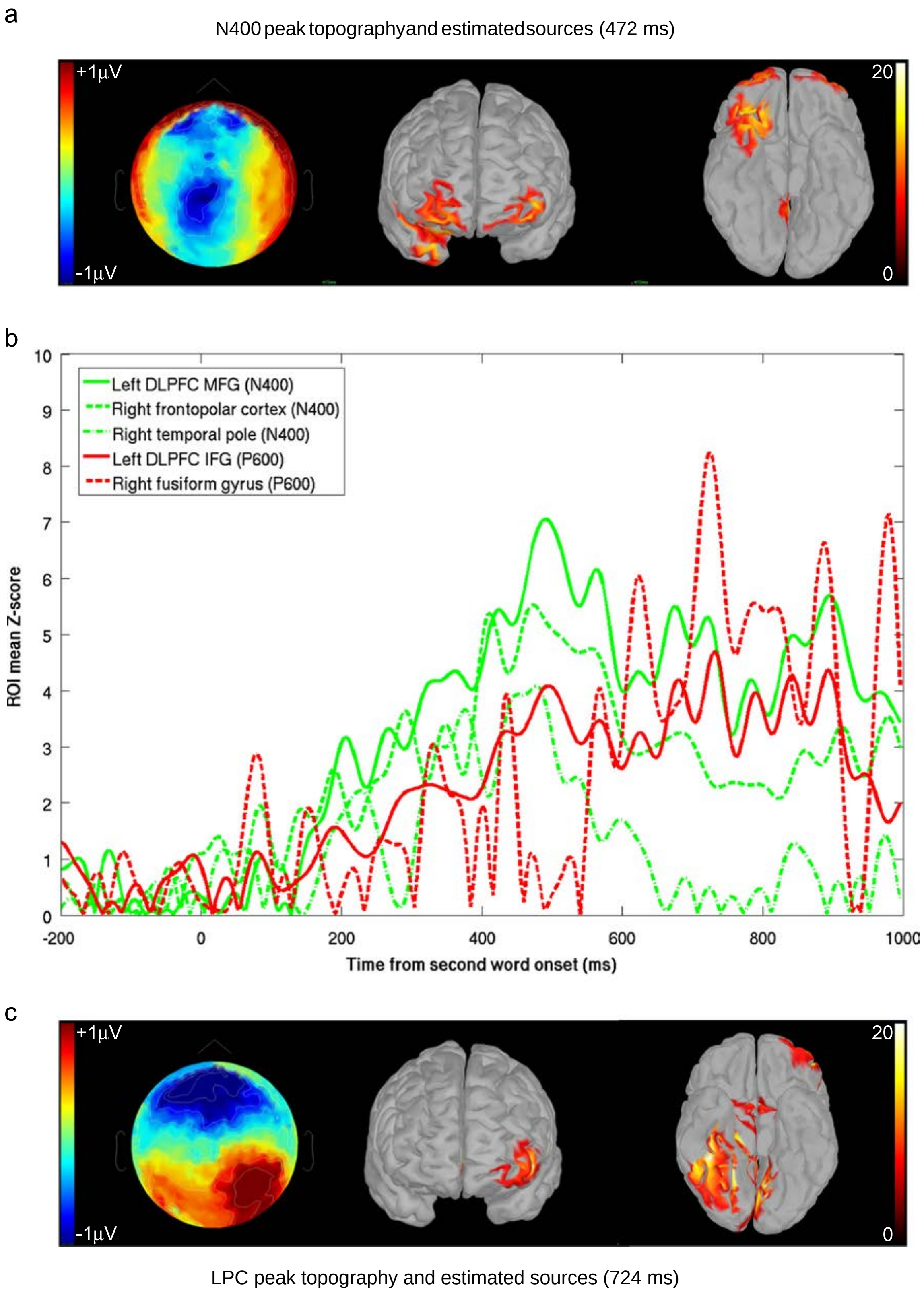

Fig. 4. Cortical sources of N400 and LPC in controls (a) N400 estimated cortical sources at the peak of the effect (472 ms). (b) Time-courses of Z-scores (computed in reference to a 200 ms baseline) respectively for N400 sources in green (left DLPFC MFG, right frontopolar cortex and right temporal pole), and for LPC sources in red (left DLPFC IFG and right fusiform gyrus) and (c) LPC estimated cortical sources at the peak of the effect (724 ms).

moderate left-lateralization (see Fig. 2). Its estimated sources were located in frontal and temporal structures, in particular in the right fronto-polar cortex, in the left DLPFC (middle frontal gyrus) and in the right temporal pole (see Fig. 4). This pattern matches the seminal description of the N400 time-course. As reviewed by Kutas and Federmeier (2011) the N400 usually corresponds to: "*a wave of activity starting at* 250 ms *in the posterior half of the left superior temporal gyrus, spreading first forward and ventrally to the*

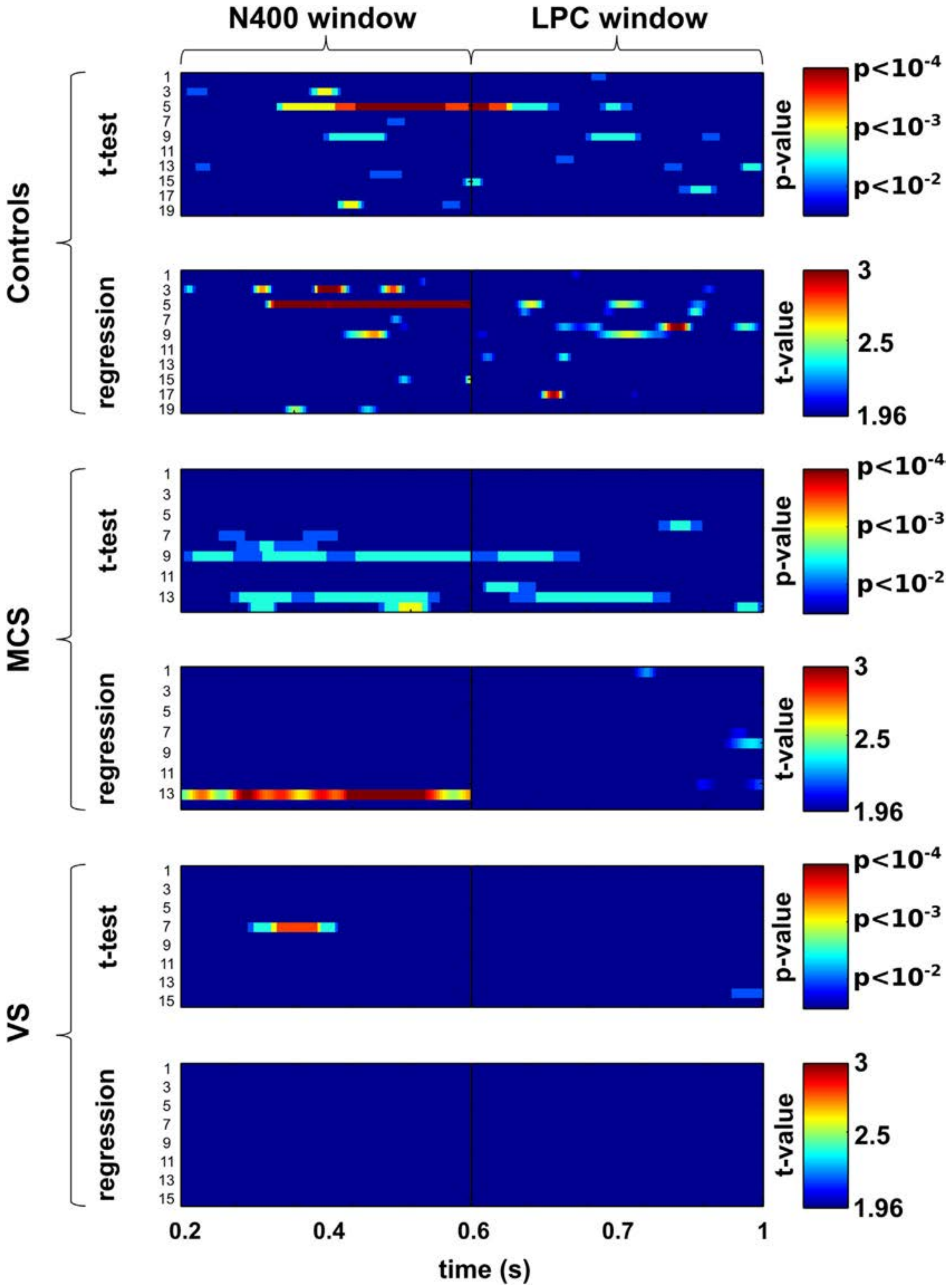

Fig. 5. Individual ERP results of semantic congruity in controls and in patients Each line corresponds to one subject (one of the 19 controls, 14 MCS patients or 15 VS patients). Congruity effects significant at the individual level are color-coded, both for the triple-threshold ("*t*-test") and the regression ("regression") approaches.

left temporal lobe by 365 *ms, and thereafter, between* 370 *and* 500 ms, *to the right anterior temporal lobe and to both frontal lobes*". When we inspected the estimated sources of the N400 we also observed an early activation in the left inferior temporal region, a region involved in supramodal word processing (Cohen et al., 2004; Price, 2012). This source was activated earlier than the significant N400 effect. Hence one may wonder whether the absence of syntactic structure of our stimuli suppressed both early syntactic processes (ELAN) and early component of the N400 which could be related to syntactic or lexico-syntactic processes. Under this view, our finding could be interpreted as a more specific correlate of lexico-semantic processing, independently of other parameters such as those implicated by the existence of a syntactic structure. This hypothesis would deserve additional studies using more reliable functional brain-imaging techniques, such as fMRI or SEEG recordings. In addition, it is interesting to note that previous studies underlined the importance of right-hemisphere temporal and frontal structures in semantic processing, in particular when complex sentences, metaphors or idioms were used (St. George et al., 1999). These authors reported fMRI activations within the right temporal lobe in response to titled paragraphs as compared with untitled paragraphs, suggesting a specific role of this region in global semantic processing.

The second correlate of semantic congruity was the LPC (or P600), which appeared as a late and sustained posterior positive complex spanning from ~700 ms to 1000 ms after the onset of the second word. Its estimated sources were mostly located in the left DLPFC (inferior frontal gyrus) and the right fusiform gyrus (see Fig. 4). While early studies described this ERP component as a marker of syntactic violation (Friederici and Meyer, 2004), recent studies challenged this interpretation by showing LPC in response to semantic violations or anomalies in the absence of any syntactic violation (Grieder et al., 2012; Hill et al., 2002). In addition, a LPC could be recorded in response to various manipulations of verbal semantics such as inversion of causality (e.g. "*the cat that fled from the mice*", (Van Herten et al., 2005)), metaphors (De Grauwe et al., 2010) or ironic stimuli (Regel et al., 2011; Spotorno et al., 2013). We propose that the LPC (or P600) could reflect conscious access to the semantic violation, whereas the N400 would reflect an earlier and non-conscious stage of semantic processing. This hypothesis is supported by 2 main arguments. First, many studies using both auditory and visual stimuli support a two-stage model of word perception, with an early non-conscious stage followed by a later stage requiring a conscious access (Gaillard et al., 2009; Marinkovic et al., 2003). While the early stage is usually restricted to localized brain networks (e.g.: MMN, early visual processing), the late stage is associated with a brain-scale increase in functional connectivity. This two-stage hypothesis is part of several models of conscious access including the global workspace model of consciousness (Dehaene et al., 2006; Dehaene and Naccache, 2001; Lamme, 2006; Sergent and Naccache, 2012). The second argument supporting our hypothesis concerns the LPC component itself. While the latency and topography of the N400 are very different from those of earlier stages of perceptual processing (e.g. the right fusiform N170 for faces; the left fusiform N200 for printed words; the MMN for deviant sounds in odd-ball paradigms), the LPC shares a latency (~200 ms after first-stage processing) and a scalp-topography reminiscent of the P3b. Given that this P3b event has been described as a specific marker of conscious access to visual stimuli (Sergent et al., 2005). This similarity between the LPC and the P3b would therefore suggest that the LPC is a neural marker of conscious semantic processing.

Interestingly, this theoretical interpretation is supported by previous works originating from memory studies. Indeed, the LPC component has been associated with conscious recollection of words (Düzel et al., 1997; Petten et al., 1991). For instance, (Düzel et al., 1997) used a "remember/know" paradigm and reported that the LPC was present exclusively for consciously remembered words. In 2003, (Misra and Holcomb, 2003) used a repetition priming paradigm with both masked and unmasked prime words preceding unmasked target words. While the N400 was attenuated both for the masked and unmasked repetition priming conditions, a significant increase of the LPC component was exclusively observed in the unmasked repetition priming condition. Note also that if the LPC observed in our work was related to conscious recollection, this would still require a semantic stage in order to explain why incongruent pairs would be better memorized than congruent ones. In order to better assess this issue, we analysed separately the LPC in first and second experimental blocks. Using our triple-threshold procedure, a significant LPC was observed both in the first and in the second blocks (both $ps < 0.05$).

In spite of their impact on our fundamental understanding of verbal semantic processing, our findings were not as powerful as we could expect, which may limit their clinical applications. Only 11/19 (58%) conscious controls showed a significant effect within the respective temporal windows of the N400 or of the LPC. In contrast, we could identify a significant P3b component in response to violations of auditory regularities in 100% of control subjects tested in the "local–global" test (Bekinschtein et al., 2009; Faugeras et al., 2012; King et al., 2013). This lack of sensitivity at the individual level may reflect a large inter-trial variability in the precise timing of semantic processing. While our results are in line with robust research requirements at the group-level by finding traditional effects in controls, the absence of systematic detection of N400 or LPC effects at the individual-level is problematic, in particular for a translational goal aiming at using these measures to improve patients' evaluation. Even within control subjects, we observed a large variability in the topography of the N400 (only 5/8 subjects with a typical N400 topography), and of the LPC (3/9 subjects with a typical LPC topography). In order to boost the N400 and LPC, we could use active tasks focused on semantic attributes of word pairs, rather than instructing subjects to simply attend to the stimuli without engaging in any specific task. Indeed, (Cruse et al., 2014) designed three experiments in normal controls, and showed that while N400 could be detected at the single-subject level in a semantically related word-pair paradigm using an active response task in 75% (9/12) of subjects, this proportion dropped to 58% (7/12) when subjects were instructed to simply pay attention to the semantic relation covertly, and to 0% when they were asked to passively listen to the material. Then in a second experiment, they showed that the use of word-pair stimuli generated from normative associations – as done in our work – increased the detection of N400 in the passive condition in 50% of subjects. Interestingly, the use of cloze sentences proved to be less effective (17%) than word pairs, which is not intuitive given the stronger semantic expectations elicited by a sentence induced context than by a single word. Indeed, verbal semantic brain activations has been reported with PET and fMRI in a few patients using sentences (see Section 1.2). Clearly, this issue of word-pairs versus sentence paradigms still requires additional studies because many factors distinguish these two paradigms, and their respective impact are not necessarily easy to predict. For instance, working memory and language impairments in patients may explain both patterns of differential results: on the one hand, sentences could be processed less efficiently than word-pairs, but alternatively, the cumulative added contextual "strength" provided by a sentence might be sufficient to overcome this deficit, and induce efficient top-down semantic processes. Our current results in controls are close the ones of this second experiment of Cruse et al.

This importance of using an active task is also coherent with our own previous results with the "local global" task. Indeed, the P3b response to the auditory rule violation ("local global" test) can be observed in a passive condition comparable to the one we used in the present study, but is considerably enhanced when subjects are asked to detect and count rule violations (Bekinschtein et al., 2009; King et al., 2013; Wacongne et al., 2011). This finding has been reliably observed in many "active paradigms", in particular when testing patients suffering from disorders of consciousness (Owen et al., 2009; Schnakers et al., 2008). Additionally, it is possible that the use of more complex and meaningful stimuli containing also syntactic structures, – such as short sentences or idioms – , may be more efficient.

4.2. *Verbal semantic processing in non-communicating patients*

At the group-level, we could detect a significant N400-like response in DOC patients. This ERP response peaked earlier than the N400 observed in conscious controls (280–314 ms in DOC patients versus 436–516 ms in controls), and its topography resembled only partially the normal N400. Indeed, whereas a clear central negativity was present in DOC patients, both the ROI and the regression analyses showed only marginal values of similarity with the canonical N400. Concerning the earlier latency of patients' N400, we note that across the 6 previous studies conducted in DOC patients one found a discretely delayed (< 20 ms) latency of N400 for incongruent trials (Balconi et al., 2013), whereas no specific information was reported in the other 5 articles (Kotchoubey, 2005; Kotchoubey, et al., 2005; Rämä et al., 2010; Schoenle and Witzke, 2004; Steppacher et al., 2013). Larger series of patients with homogenous aetiologies would be necessary to establish reliable landmarks on this issue, as it is plausible that different aetiologies should be associated to different patterns of impairments of the brain's semantic networks. Concerning the topography of the N400 in the DOC group, – and in the VS and MCS subgroups – , we mostly retain its overall similarity with the normal pattern, and do not emphasize the left-right asymmetry observed in the MCS group. Larger and more homogeneous samples of patients seem necessary to establish a stable picture of the results. The result which most deserves to be highlighted is the confirmation that a N400 effect can be observed in vegetative state patients.

In sharp contrast with the N400, the LPC was absent in the VS patients group. This is remarkable because the LPC was observed in the MCS group with a latency and a topography highly similar to those observed in the group of controls. This result strongly supports our proposal that the LPC may be a specific marker of conscious access to semantic attributes. It is also coherent with our previous finding that only conscious and MCS patients showed a late P3b response indexing the conscious detection of violations of a long-range auditory rule (Bekinschtein et al., 2009; Faugeras et al., 2012; King et al., 2013). As previously mentioned, many studies conducted in the visual modality extended the validity of this two-stage model of conscious perception (Gaillard et al., 2009; Sergent et al., 2005). Moreover, our finding of a significant LPC in MCS patients further confirm the relevance of this recently defined clinical category (Giacino et al., 2002; Kalmar and Giacino, 2005). Indeed, if the LPC is a signature of the active maintenance of information in a brain-scale coherent network corresponding to conscious perception, then its presence in MCS patients would confirm the presence of conscious states in those patients. This claim is also supported by our recent report that MCS patients present, – like conscious patients – significant long-range functional connectivity, as measured with a new mathematical measure (weighted Symbolic Mutual Information, wSMI), whereas this property is massively impaired in VS patients (King et al., 2013).

At the individual level, our results were restricted by the limited sensitivity of the N400 and LPC to verbal semantic processing in controls. The N400 was mostly detected in MCS, while only a single VS patient (who later recovered consciousness and functional communication) showed this response. This finding corroborates previous reports showing a more reliable N400 in MCS than in VS (Schoenle and Witzke, 2004; Steppacher et al., 2013). We found a similar pattern for the LPC component. However, the comparison of both group-level and individual results lead us to propose a distinct explanation for the similarity of individual results of these two ERP components. In the light of our theoretical distinction between the two successive stages of perception, the extreme rarity of LPC in VS patients may reflect a qualitative difference between VS and MCS patients dependent on the presence/absence of a conscious access to a semantic representation. In contrast, the similarly low proportion of N400 in VS patients as compared to MCS patients may rather reflect a quantitative difference: the early stage of unconscious semantic processing may be weaker but still present in some VS patients.

Finally, we could compare the diagnostic and prognostic value of five distinct ERP responses. The inspection of these 5 ERP correlates is suggestive of a “Jacksonian” hierarchical organization, from low-level automatic events (P1 and MMN) to high-level cognitive processes (N400, LPC and global effect) more related to functional communication and to conscious processing. Indeed, the two late ERP components (the global effect and the LPC) were systematically observed in patients also showing preserved P1 and MMN responses, while many patients showed only the early or automatic responses. This was also true for the N400 responses, which were systematically observed in patients with preserved P1 and MMN responses. However, the relative dissociation between N400, LPC and global effect may reflect a diversity of high-level cognitive processors, which may operate independently.

In conclusion, we note that the LPC observed in controls and in MCS groups shares many properties of the P3b responses reported in other auditory or visual paradigms during conscious access to perceptual representations. On the basis of these findings and the two-stage model of perception, we proposed to identify the LPC with a conscious stage of semantic processing of verbal stimuli.

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Appendix A. Supplementary Information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2014.10.014.

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1.3 Supplementary material

Table S1. Free association rates of congruent word pairs:

Primes	Targets	Free association rate (%)	Primes	Targets	Free association rate (%)
abstrait	concret	84	girafe	cou	60,7
album	photo	92,1	haine	amour	38
allumette	feu	66,3	heure	minute	39
ancien	vieux	50	hibou	nuit	42,7
araignée	toile	40,3	homme	femme	84
banque	argent	57	humour	rire	29
beau	laid	33	isolement	seul	39
berceau	bébé	68,5	laitue	salade	69,7
bureau	travail	47,2	lent	rapide	54
cartable	école	57,3	lourd	léger	37
chaise	table	34,8	luge	neige	74,1
ciseaux	couper	73	marteau	clou	40,4
cité	ville	43	matin	soir	30
classique	musique	52	mensonge	vérité	28
collier	perle	41,5	occident	orient	61
coq	poule	56,1	propre	sale	50
couronne	roi	39,3	puissance	force	30
crabe	pince	45	rage	colère	36
crainte	peur	79	raquette	tennis	88,7
croyance	religion	31	réveil	matin	55
démon	diable	39	ruche	abeille	82
distance	loin	30	senteur	parfum	31
douleur	mal	29	serrure	clef	70,7
écrou	vis	43,8	soif	eau	32
enfer	paradis	30	sombre	clair	30
erreur	faute	41	songe	rêve	63
excuse	pardon	36	tomate	rouge	49,5
flèche	arc	52,8	tonneau	vin	73
football	ballon	40,4	toupie	tourner	43,8
fourchette	couteau	49,4	tranquille	calme	30
frigo	froid	42,7	vache	lait	42,7
froid	chaud	47	valise	voyage	43,8
gaieté	joie	50	vase	fleur	63

Adapted from (Alario & Ferrand, 1998; Ferrand, 2001)

Annexe. Word pairs

n	word 1	word 2	congruency	n	word 1	word 2	congruency	n	word 1	word 2	congruency	n	word 1	word 2	congruency
1	ruche	abeille	CG	35	vase	poule	ICG	69	crainte	peur	CG	103	gaieté	ville	ICG
2	luge	abeille	ICG	36	coq	poule	CG	70	propre	peur	ICG	104	cité	ville	CG
3	ruche	neige	ICG	37	frigo	froid	CG	71	crainte	sale	ICG	105	guerre	paix	CG
4	luge	neige	CG	38	couronne	froid	ICG	72	propre	sale	CG	106	soif	paix	ICG
5	flèche	arc	CG	39	frigo	roi	ICG	73	grand	petit	CG	107	guerre	eau	ICG
6	crabe	arc	ICG	40	couronne	roi	CG	74	froid	petit	ICG	108	soif	eau	CG
7	flèche	pince	ICG	41	vache	lait	CG	75	grand	chaud	ICG	109	démon	diable	CG
8	crabe	pince	CG	42	chaise	lait	ICG	76	froid	chaud	CG	110	senteur	diable	ICG
9	cartable	école	CG	43	vache	table	ICG	77	abstrait	concret	CG	111	démon	parfum	ICG
10	tranquille	école	ICG	44	chaise	table	CG	78	excuse	concret	ICG	112	senteur	parfum	CG
11	cartable	calme	ICG	45	réveil	matin	CG	79	abstrait	pardon	ICG	113	haine	amour	CG
12	tranquille	calme	CG	46	laitue	matin	ICG	80	excuse	pardon	CG	114	banque	amour	ICG
13	berceau	bébé	CG	47	réveil	salade	ICG	81	songe	rêve	CG	115	haine	argent	ICG
14	marteau	bébé	ICG	48	laitue	salade	CG	82	rage	rêve	ICG	116	banque	argent	CG
15	berceau	clou	ICG	49	hibou	nuit	CG	83	songe	colère	ICG	117	lourd	leger	CG
16	marteau	clou	CG	50	toupie	nuit	ICG	84	rage	colère	CG	118	sombre	leger	ICG
17	serrure	clé	CG	51	hibou	tourner	ICG	85	occident	orient	CG	119	lourd	clair	ICG
18	girafe	clé	ICG	52	toupie	tourner	CG	86	isolement	orient	ICG	120	sombre	clair	CG
19	serrure	cou	ICG	53	bureau	travail	CG	87	occident	seul	ICG	121	croyance	religion	CG
20	girafe	cou	CG	54	collier	travail	ICG	88	isolement	seul	CG	122	football	religion	ICG
21	ciseaux	couper	CG	55	bureau	perle	ICG	89	lent	rapide	CG	123	croyance	ballon	ICG
22	tonneau	couper	ICG	56	collier	perle	CG	90	beau	rapide	ICG	124	football	ballon	CG
23	ciseaux	vin	ICG	57	tomate	rouge	CG	91	lent	laid	ICG	125	enfer	paradis	CG
24	tonneau	vin	CG	58	valise	rouge	ICG	92	beau	laid	CG	126	humour	paradis	ICG
25	fourchette	couteau	CG	59	tomate	voyage	ICG	93	classique	musique	CG	127	enfer	rire	ICG
26	raquette	couteau	ICG	60	valise	voyage	CG	94	puissance	musique	ICG	128	humour	rire	CG
27	fourchette	tennis	ICG	61	album	photo	CG	95	classique	force	ICG	129	distance	loin	CG
28	raquette	tennis	CG	62	écrou	photo	ICG	96	puissance	force	CG	130	mensonge	loin	ICG
29	allumette	feu	CG	63	album	vis	ICG	97	ancien	vieux	CG	131	distance	vérité	ICG
30	araignée	feu	ICG	64	écrou	vis	CG	98	erreur	vieux	ICG	132	mensonge	vérité	CG
31	allumette	toile	ICG	65	homme	femme	CG	99	ancien	faute	ICG	133	matin	soir	CG
32	araignée	toile	CG	66	heure	femme	ICG	100	erreur	faute	CG	134	douleur	soir	ICG
33	vase	fleur	CG	67	homme	minute	ICG	101	gaieté	joie	CG	135	matin	mal	ICG
34	coq	fleur	ICG	68	heure	minute	CG	102	cité	joie	ICG	136	douleur	mal	CG

CG: congruent or semantically related word pair
ICG: incongruent or semantically unrelated word pair

2 Deuxième article: *Unconscious semantic processing is not automatic: the case of polysemous words*

2.1 Présentation de l'article

Dans ce deuxième article, nous avons voulu revisiter un travail original de l'un des pionniers de l'exploration de la sémantique inconsciente, Anthony Marcel. Ses travaux sur le traitement sémantique des mots polysémiques (mots qui possèdent au moins deux sens indiscernables par leur orthographe ou leur prononciation) suggéraient en effet des différences qualitatives notables selon qu'ils soient perçus consciemment ou non (Marcel, 1980). Dans une situation de perception consciente, la représentation activée d'un mot polysémique dépendrait fortement du contexte. Ce contexte peut être le mot qui précède le mot polysémique. Par exemple, alors qu'« avocat » aura un effet d'amorçage sémantique sur « juriste » dans la séquence « médecin-avocat-juriste », il n'aura aucun effet dans la séquence « salade-avocat-juriste ». Les résultats de Marcel suggèrent qu'à l'inverse, en situation non consciente (le mot polysémique étant masqué), les deux représentations du mot seraient activées permettant ainsi un effet de d'amorçage dans une séquence telle que « salade-avocat-juriste ».

Souvent cités[9], ces résultat n'ont cependant à notre connaissance jamais été répliqués. Or en plus de l'intérêt scientifique fondamental relatif à la teneur des représentations mentales non conscientes, ces résultats laissent entrevoir de nouvelles perspectives d'évaluation de patients présentant un trouble de la conscience en explorant à la fois leurs capacités de traitement sémantique et leur niveau de conscience.

Cet article comporte 3 expériences comportementales, la dernière associant au comportement l'enregistrement des potentiels évoqués. Comme nous allons le voir la dissociation proposée par Marcel ne correspond pas aux résultats que nous avons obtenus.

2.2 Article 2

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[9] On en dénombre 158 dans Google Scholar, ce travail ayant été publié dans un livre, le nombre de citation est difficile à quantifier plus précisément.

Unconscious semantic processing is not automatic: the case of masked polysemous words

Benjamin Rohaut[1234], F-Xavier Alario[5], Jacqueline Meadow[23], Laurent Cohen[1234], Lionel Naccache[12346*]

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Affiliations :

1 AP-HP, Groupe hospitalier Pitié-Salpêtrière, Department of Neurology, Paris, France
2 INSERM, U 1127, F-75013, Paris, France
3 Institut du Cerveau et de la Moelle épinière, ICM, PICNIC Lab, F-75013, Paris, France
4 Sorbonne Universités, UPMC Univ Paris 06, Faculté de Médecine Pitié-Salpêtrière, Paris, France
5 Laboratoire de Psychologie Cognitive-UMR 7290, Centre National de la Recherche Scientifique (CNRS), Aix Marseille Université Marseille, France
6 AP-HP, Groupe hospitalier Pitié-Salpêtrière, Department of Neurophysiology, Paris, France

*** Corresponding author:** lionel.naccache@gmail.com

Abstract

Semantic processing of visually presented words can be identified both on behavioral and neurophysiological evidence. One of the major discoveries of the last decades is the demonstration that these signatures of semantic processing, - initially observed for consciously perceived words -, can also be detected for masked words inaccessible to conscious reports. In this context, the distinction between conscious and unconscious verbal semantic processing constitutes a challenging scientific issue. A prominent view considered that while conscious representations are subject to executive control, unconscious ones would operate automatically in a modular way, independent from control and top-down influences. Recent findings challenged this view by revealing a strong influence of endogenous attention and task-setting on unconscious processing. However, one of the major arguments supporting the automaticity of unconscious semantic processing originates from a seminal observation reported by Marcel in 1980 about polysemous words. In the present study we present a combination of behavioral and event-related-potentials (ERPs) results that refute this view by showing that the current conscious semantic context has a major and similar influence on the semantic processing of both visible and masked polysemous words. In a classical lexical decision task, a polysemous word (Word-2 or W2) was preceded by a word (Word-1 or W1) which defined the current semantic context. Crucially this context was associated with only one of the two meanings of the polysemous word, and was followed by a word/non-word target. Behavioral and electrophysiological evidence of semantic priming of target words by masked polysemous words was strongly dependent on the conscious context. Moreover, we describe a new type of influence related to the response-code used to answer to target words in the LDT. Unconscious semantic priming constrained by the conscious context was present both in behavior and ERPs exclusively when right-sided subjects responded with their right hand to words. The strong and respective influences of conscious context and response-code on semantic processing of masked polysemous words demonstrate that unconscious verbal semantic representations are not automatic.

Introduction

During the last decades, the scope of unconscious cognitive processes has been dramatically enlarged (Kihlstrom 1987; Dehaene and Naccache 2001; Naccache 2006; Dehaene 2014). This major conceptual change, - grounded on a rich set of original empirical findings collected in normal volunteers and in brain-damaged patients -, affects both the representational content of unconscious processes, and their relation to top-down executive control. Schematically, within this relatively short period the dominant view moved from a modular (Fodor 1983), automatic (Schneider and Shiffrin 1977) and ‘stupid’ unconscious, to a heterogeneous unconscious which includes flexible (Naccache 2008; Van den Bussche, Segers et al. 2008) and high-level cognitive processes (Naccache and Dehaene 2001; Naccache, Gaillard et al. 2005; Kouider and Dehaene 2007) sensitive to various influences including: endogenous spatio-temporal attention (Kentridge, Heywood et al. 1999; Naccache, Blandin et al. 2002; Kentridge, Nijboer et al. 2008), conscious consideration of task instructions and stimuli sets (Greenwald, Abrams et al. 2003), and executive control (van Gaal, Ridderinkhof et al. 2008; van Gaal, Ridderinkhof et al. 2009).

This recent conceptual evolution culminated in empirical reports showing that semantic attributes of recent symbolic stimuli (such as written words and numbers) can be processed unconsciously and can be sensitive to executive control (for a short review see (Naccache 2008)). However, this issue is still debated both on methodological and theoretical grounds (Holender 1986; Abrams and Greenwald 2000; Kouider and Dupoux 2004).

In the present study we specifically addressed this crucial debate: how deep can written words can be unconsciously processed in conscious subjects, and are these high-level cognitive processes sensitive to conscious context?

In order to tackle this issue empirically we decided to revisit, - more than 30 years later -, the seminal work of Marcel exploring the unconscious semantic processing of polysemous words (Marcel 1980). In this set of experiments, Marcel used the word priming paradigm initially designed by Meyer and Schvaneveldt (Meyer and Schvaneveldt 1971). More specifically, Marcel exploited an important result previously found by these two authors (Schvaneveldt and Meyer 1976) in a lexical decision task (LDT): they used a three word trial structure beginning with a context word (W1), followed by a prime word (W2) and then by a target stimulus which could be a word or a pseudo-word. Crucially, W2 was a polysemous word (e.g.: BANK conveying at least two distinct semantic representations). They showed that the contextual word W1 (e.g.: SAVE) had a radical impact on W2 priming effects on the target word. Only the semantic representation congruent with the context defined by W1 (e.g.: SAVE-BANK) primed a semantically related target word (e.g.: MONEY). In sharp contrast, the meaning incongruent with the context did not prime semantically related target words (e.g.: RIVER-BANK-MONEY). This result demonstrated the strong influence of conscious context on conscious priming effects (priming for unmasked primes). Since this pioneering article, several studies replicated and refined the influences of context on meaning selection (Swinney, Onifer et al. 1979; Tanenhaus, Leiman et al. 1979; Simpson 1981; Simpson and Krueger 1991; Paul, Kellas et al. 1992; Tabossi and Zardon 1993; Chen and Boland 2008). A recent study extended this effect by reporting some of its ERP correlates (Kotchoubey and El-Khoury 2014)

Inspired by this work, and driven by his current studies on masked semantic priming (Marcel 1983), Marcel used this triple-word paradigm designed by Schvaneveldt and Meyer to present unmasked and masked polysemous W2 words. Whenever W2 was unmasked, Marcel replicated the original finding that only the contextualized meaning of W2 has a priming effect. Furthermore, he discovered that when W2 was masked, both its contextualized and its non contextualized meanings primed the target word. This finding suggested the existence of a qualitative difference between conscious and unconscious representations: while conscious semantic processing is associated with a reduction of polysemy to a single representation relevant to the current context, unconscious processing enables the activation of multiple parallel semantic representations irrespective of working memory content.

Given the theoretical importance of this finding, and given the recent discovery of multiple sources of top-down influences on unconscious perception, we revisited this paradigm and took into account the various methodological concerns raised by these early works (see for instance the introduction of (Naccache, Gaillard et al. 2005)). We included both subjective and objective measures of conscious visibility, and used shorter W2-Target stimulus-onset asychronies (SOAs) considering the fast decay of unconscious priming effects (Greenwald 1996; Rossetti 1998; Naccache, Blandin et al. 2002). We also used distinct lists of words for masked and unmasked stimuli, in order to circumvent the misinterpretation of non-semantic masked priming effects as being semantic, through the automatization of stimulus-response codes bypassing semantic analysis (Abrams and Greenwald 2000 ; Naccache and Dehaene

2001 ; Naccache, Gaillard et al. 2005). We manipulated top-down influence on masked W2 stimuli through two factors: semantic context as defined by consciously visible words W1, and response instructions. In most LDT experiments, subjects are typically instructed to categorize targets as words by pressing a response button their right-hand, and to categorize pseudo-words with their left hand (Weems and Zaidel 2005). We decided to test the effect of response-code manipulation on the processing of masked primes. Finally, we used both behavioural and ERP measures in order to gain access to a fine-grained description of the dynamics of masked W2 processing.

In a series of three experiments we demonstrate that unconscious semantic processing of masked polysemous words does exist, but is highly dependent on these two sources of influence.

2. Experiments

2.1. Experiment 1

In the first experiment, we adapted the original paradigm of Marcel in order to study, in a LDT, both conscious (unmasked) and unconscious (masked) semantic priming elicited by polysemous words W2 contextualized by a consciously visible word (W1).

2.1.1. Material and Methods

Participants

Thirty-two right-handed native French speakers volunteered to this study (mean age = 23.47 years +/- 4.36; sex ratio = 10 males /22 females). They had no neurological or psychiatric history, were free of any medication and had normal or corrected to normal vision. All participants gave written informed consent, and the experiment was approved by the Ethical Committee of the Kremlin-Bicêtre hospital APHP (n°98-25).

Materials

The material used for this lexical decision task experiment was inspired by Marcel (1980). One hundred polysemous words (W2), with a length varying between three and eight letters, were selected from French dictionaries (‘Le Robert’ and ‘Larousse’ dictionaries). Among them, we first selected 40 polysemous nouns with two frequent and clearly distinct meanings. Each polysemous word was then associated with two contextual words (W1), and with two target (Tgt) nouns, each associated with one of the two meanings of W2 (see Table 1 for a detailed description of lexical characteristics). Given the lack of a French database reporting the frequencies of the different meanings of polysemous words, and given the insufficient number of polysemous words in French free-association databases, we generated one W1 and one Tgt for each of the two meanings of W2. Then each polysemous W2 was paired with another semantically unrelated W2, yielding the following five experimental conditions (see Figure 1a & Supplementary Table 1a):

- *Congruent (Cg):* W1 and Tgt are associated to the same meaning of the polysemous W2; (e.g.: *Hand-Palm-Wrist).*
- *Incongruent (Icg):* W1 and Tgt are associated to different meanings of the polysemous W2 (e.g.: *Hand-Palm-Tree).*

- *Initial (Init):* W1 only is associated to one meaning of the polysemous word (e.g.: *Hand-Palm-Shore).*
- *Separate (Sep):* W2 is neither associated to W1 nor to Tgt, but W1 is associated to Tgt (e.g.: *River-Palm-Shore).*
- *Terminal (Ter):* Tgt is associated to one of the two meanings of polysemous W2 (e.g.: *River-Palm-Wrist).*

This design allowed for the generation of 400 distinct trials (40 W2 X 5 conditions X 2 meanings). The frequencies of the two target words associated to W2 words did not differ (p value of Student t-test =0.84). In order to create the trials with pseudo-words we followed Marcel's approach. We used a second list of 40 words drawn from the original list of 100 polysemous words. These 40 words were combined similarly to the previous one, also generating 400 trials. On half of these trials the target consisted in a pseudo-word (see Supplementary table 1b). Forty pronounceable pseudo-words (pseudo-nouns) were generated with the Lexique toolbox (http://www.lexique.org) (New, Pallier et al. 2004), matching the length of the real words targets (4-8 letters; mean=6.8). Those two lists ensured that the presence of a semantic link between W1 and W2 was not predictive of the word/pseudo-word status of the target word. Note however that even if every trial was presented only once, words from the experimental list were always associated to target words. A total number of 800 trials was obtained, with a pseudo-word probability of 0.25. The masked and unmasked conditions were used in two different sessions. In order to prevent subjects from transferring stimulus-response associations from unmasked to masked trials, - which could lead to non-semantic priming effects (Abrams and Greenwald 2000 ; Naccache and Dehaene 2001) -, half of the critical material originating from the first list of 400 trials was presented in the masked session, while the second half was used in the unmasked session. Therefore for a given subject, masked polysemous words were never seen as unmasked words. These two sub-lists were counterbalanced across subjects, as well as the order of the masked and unmasked sessions, and right/left motor response instructions in the lexical decision task, leading to 8 different combinations. Finally, we decided to avoid that a given word W2 would be systematically contextualized in one of its two meanings across subjects. To avoid this possible bias, we inverted lists of these 8 combinations of trials across subjects. Thus, the experiment is designed for numbers of subjects which are multiples of 16. We tested 32 volunteers. For each subject, trials were pseudorandomized using Mix software (van Casteren and Davis 2006) in such a way that no word could appear twice in any 10 consecutive trials.

Procedure and design

Each trial began with the presentation of a context word (W1), followed by a polysemous word (W2) and then by a target word/pseudo-word (Tgt) (see Figure 1b). Subjects had to perform a lexical decision task (LDT) on Tgt by pressing left or right hand buttons with their index. Each subject followed one set of motor response instruction (answer to words with the right button and to pseudo-words with the left button, or the opposite), and instructions were counterbalanced across subjects. Stimuli timing was different for unmasked and masked conditions. In the unmasked condition the three stimuli (W1, W2, Tgt) were each presented for 200ms with W1-W2 and W2-Tgt SOAs of 500ms. In the masked condition, we used the following stimulus structure: W1 was presented for 200ms and was followed by a sandwich masking sequence (pre-mask for 33ms -W2 for 33 ms – post-mask for 83ms) which preceded the presentation of the Tgt for 200ms. Pre-masks and post-masks consisted in strings of 8 random upper case consonants. Note that the values of the W2-Tgt SOA were 500 ms in the unmasked condition and 116 ms in the masked condition. Those values were chosen in order to maximize the chance of observing a subliminal priming effect, given the usually short-lived representations elicited by masked stimuli (Greenwald 1996). A central fixation cross was presented for 300ms before W1 and W2 onsets. Subjects performed a short training session (20 trials) before each of the two (masked and unmasked) sessions. The order of masked and unmasked sessions was counterbalanced across subjects. Each subject was tested on 800 trials, with a pause every 80 trials. At each pause, a feedback was delivered in order to reinforce subjects' performances (average response-time and accuracy). The experiment lasted about 60 minutes. Subjects were seated at a distance of 50 cm from a 13'' HP® color high-resolution RGB monitor (60Hz refresh rate), and were instructed to maintain their gaze on the center of the screen throughout the experiment. Stimuli were displayed in white on a black background, in lower case ''Time new roman'' font, with a size of 14. After the completion of the main experiment subjects had to answer to a brief questionnaire assessing: i) the subjective visibility of masked stimuli; ii) subjects' detection of the presence of within-trials semantic links between words, iii) subjects' detection of the presence of polysemous words. After this questionnaire, and in order to compute an objective index of masked stimuli discrimination (d' value), subjects were asked to perform a forced-choice LDT on the masked *Congruent* condition trials in which the masked stimulus could either be a polysemous word (the original list of 40 masked W2 words) or a pseudo-word (40 masked pseudo-words never presented in the main experiment). During this experiment subjects were instructed to respond

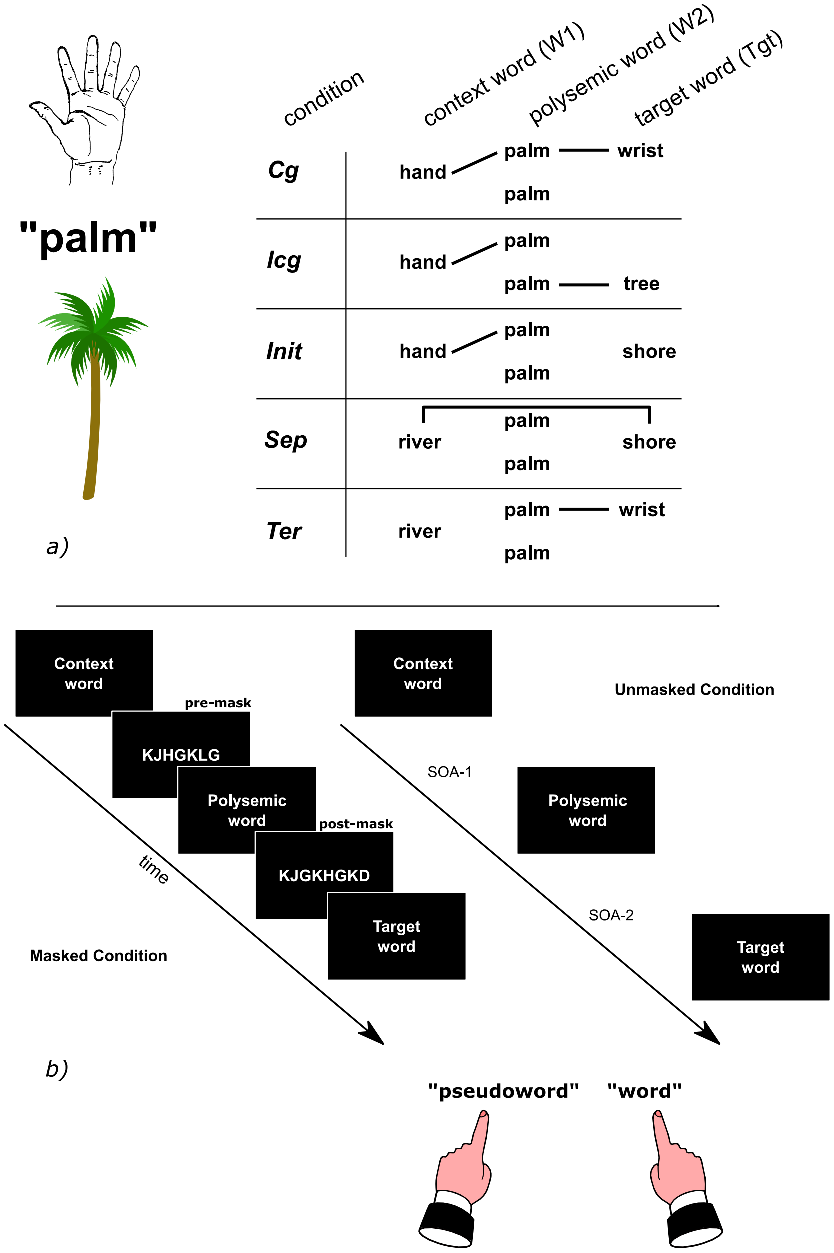


Figure 1. Experimental paradigm

Forty polysemous words (e.g: palm) were presented in a context defined by W1, and then followed by a word/pseudo-word target stimulus. Experimental trials could be either: Congruent (Cg), Incongruent (Icg), Initial (Init) Separate (Sep) or Terminal (Ter) regarding the semantic relations between words (represented by the black connector in (a).
In the Masked condition, polysemous words were immediately preceded and followed by a mask (pre-mask and post mask, see b). Stimulus onset asynchrony (SOA) were set as followed: in Experiment-1, SOA-1=500 ms, SOA-2=500 ms in Unmasked and 116 ms in Masked condition; in Experiments 2 & 3, SOA-1= 900 ms and SOA-2= 100 ms in both Masked and Unmasked conditions. Response-codes (e.g.: "right hand for words") were crossed between subjects in Experiments 1 & 2, and within subjects in Experiment 3.

with the code used during the masked block. Finally, a brief post-experiment interview probed subjects' ability to report the presence of polysemous words in the main experiment. We first asked subjects to report any comment about the words presented (W1, W2 or target words). We then explained them trial structure as well as the polysemy of W2, and asked them to report exemplars of polysemous W2.

2.1.2. Statistics

Multifactorial analyses of variance (ANOVA) were computed on median reaction times (RT) and on error rates using R 2.12.2 (Team 2011). In all ANOVAs performed in the 3 experiments we declared subjects as a random factor.

2.1.3. Results

Subjective reports about intra-trial semantic links

The vast majority of subjects (31/32; 97%) reported the presence of intra-trials semantic links between words, but very few (3/32; 9%) spontaneously reported the systematic polysemous status of W2. These 3 subjects ran the unmasked block in the second half of the experiment (probability of differences of reportability between the two possible blocks orders: χ^2=3.31, p=0.068). Once informed about W2 status, nine subjects (9/32, 28%) including the three previous subjects, were able to report between one to three polysemous words. Seven out of these 9 subjects also ran unmasked blocks in the second half of the experiment (χ^2=3.86, p=0.049). These two subjective reports findings suggest that only consciously perceived W2 stimuli could be recalled.

Response times

We first ran an ANOVA on median correct RTs with the following factors of interest: Masking (2 levels) x Semantic-link (5 levels) x Order (2 levels). A main effect of Masking was observed (F(1,31)= 20.9, p<0.001) corresponding to faster responses on unmasked trials (effect size= 34ms). However, the structure of the masked and unmasked trials differed in several respects, including W2-Tgt SOA. This effect may result from the masking of the target by post-mask which follows W2 in the masked condition. More importantly, there was no main effect of Semantic-link (F(4,124)= 1.47; p=0.22), but a marginal interaction was observed between Masking and Semantic-link (F(4,124)=2.19; p=0.07). This interaction corresponded to a trend toward a general priming effect in the unmasked condition (all conditions in which the target was preceded by a related word (Cg, Icg, Sep, Ter) as compared to *Init* trials (F(4,124)=2.25; p=0.07)), while there was no such tendency in the masked condition (F(4,124)=1.19; p=0.32). (see Figure 2a).

In order to better explore the respective weigh of W1 and W2 priming effects in the unmasked condition, we ran a second ANOVA restricted to unmasked trials using the following three factors of interest: W1-Tgt semantic priming, W2-Tgt semantic priming, as well as block-order (unmasked blocks ran before or after masked ones). We observed a main effect of W2-Tgt semantic priming (F(1,30)=8.2; p=0.008), as well as an effect of W1-Tgt semantic priming (F(1,30)=6.8; p=0.01), and a marginal trend of block-order effect (F(1,30)=2.8; p=0.10) with subjects answering faster when unmasked trials were ran first. We also found a significant triple interaction between these three factors (F(1,30)=4.95; p=0.03). This interaction reflects the existence of a pattern of results very similar to the one reported by Marcel for the unmasked W2 trials in subjects who began the experiment with unmasked W2 trials: a W2-Tgt semantic priming effect was present only for contextualized meaning of polysemous words W2 associated to W1 (see Figure 2b). In sharp contrast, both meaning of W2, - as well as of W1 -, primed target processing in subjects who performed the unmasked blocks in the second half of the experiment (see Figure 2c).

Error rates

Overall mean accuracy reached 98.66%. The same ANOVA analysis crossing: Masking (2 levels) x Semantic-link (5 levels), and including subject as a random factor revealed a main effect of masking (F(1,31)= 14.74; p<0.001). Masked trials were answered with a better accuracy than unmasked ones (99.1% vs 98.2% for unmasked trials). We also observed a trend of semantic-link effect (F(4,124)= 2.29; p=0.06), corresponding to a slightly better accuracy for Cg, Sep and Ter trials (98.8%) than for *Icg* and *Init* trials (98,4%). No interaction was found between masking and semantic-link (F(4,124)= 0.69; p=0.6). The second ANOVA did not reveal any significant effect or interaction.

Masked words visibility

After the end of the experiment, none of the subjects reported having seen masked polysemous W2 in the masked trials. Moreover, when engaged in a forced-choice discrimination task (word/pseudo-word) on masked W2 stimuli, objective discriminability did not differ from chance-level (mean d’= 0.012; C.I.=[-0.11 0.09]; t-test p value against a zero centered distribution = 0.82). No correlation was observed across subjects between on the one

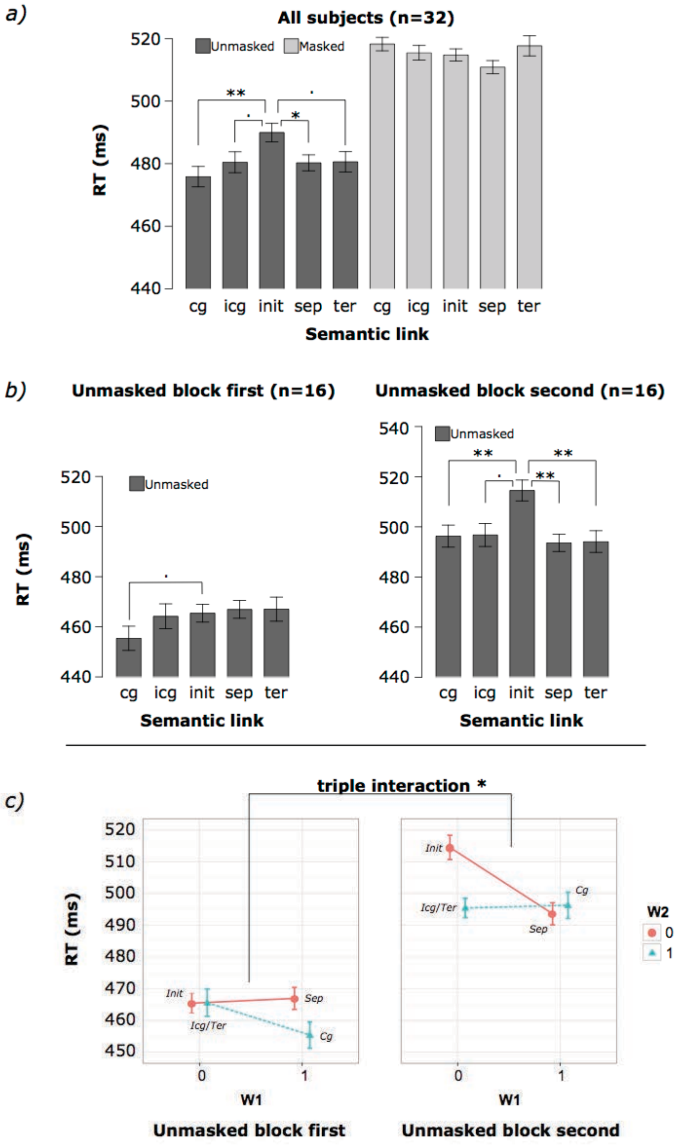


Figure 2. Semantic priming in Experiment 1

(a) Median correct RTs are plotted for each condition (Cg=Congruent, Icg= Incongruent, Init=Initial, Sep=Separate and Ter=Terminal) in masked and unmasked blocks. A semantic-link effect was present only in unmasked blocks. Bars indicate standard errors of mean; ****** = $p<0.01$; ***** = $p<0.05$; **.** = $p<0.1$. *(b) Post-hoc analyses revealed a block-order effect: subjects who performed the unmasked block in the first part of the experiment showed a priming effect limited to the contextualized meaning of the polysemous W2 (Cg), whereas subjects who performed the unmasked block in the second part of the experiment showed a semantic priming in the 4 conditions as compared to Init trials. (c) A significant triple interaction between Block-order, W1-priming and W2-priming effect was observed.*

hand the size of priming by masked W2 (Init-Cg) in the main experiment, and on the other hand the d’ value (p=0.8). Finally, the size of the priming effect interpolated for a null d’ did not differ from zero (p=0.25). Therefore both subjective reports and d’ statistics confirmed the absence of conscious perception of masked polysemous W2 in this experiment.

2.1.4. Synthesis

The results of Experiment 1 can be reduced to two main findings, concerning the processing of unmasked and masked W2, respectively. For unmasked trials, we observed two patterns of behavior, depending on block order. In subjects who began with the unmasked W2 blocks, we basically replicated the original finding of Marcel and Schvaneveldt: the semantic context established by W1 restricted the processing of polysemous W2 to its contextually associated meaning. No W2-Tgt semantic priming effect was observed in *Icg* trials. In contrast, subjects who finished the experiment with unmasked W2 words showed a pattern of results reminiscent of the one observed by Marcel for masked words. Both meanings of W2 were processed similarly, as evidenced by a W2-Tgt semantic priming effects in all conditions but *Init*. Notably, subjects who began with masked trials were slower to process unmasked trials than those who began with unmasked blocks. One may imagine that the combination of RTs slowing with a loss of inhibition on the non contextualized meaning of W2 could reflect a decrease of executive control secondary to cognitive fatigue.

For masked trials, we failed to observe any form of W2 processing, suggesting that our masking procedure was too strong. This is supported by the absence of both subjective and objective trace of W2 processing. Note also, that we failed to observe direct W1-Tgt priming effect in the masked condition (*Cg* and *Sep* conditions compared to *Init*) suggesting that the [pre-mask - W2 - post-mask] sequence interrupted the potential priming of target words by contextual W1 words.

2.2. Experiment 2

Experiment 2 was designed in order to maximize unmasked and masked semantic priming. To do so, we designed a new list of pseudo-words better matched with target words, in order to increase the necessity for subjects of adopting of semantic processing strategy during the task. Also, we increased W1 exposure to increase their influence (W1 duration = 700ms versus 200ms in Experiment 1). W2 duration was kept at 33ms, both in masked and unmasked blocks. In addition, we decreased masking strength, tested three masking conditions, and shortened the W2-Tgt SOA to 100ms, in order to capture short-lived priming effects (Greenwald 1996; Rossetti 1998; Naccache, Blandin et al. 2002). Finally, in an attempt to discard the potential role of fatigue in the block order effect reported in Experiment 1, we also decreased the total number of trials. To this end, we only used three conditions: *Congruent (Cg), Incongruent (Icg) and Initial (Init*).

2.2.1. Material and Methods

Participants

Forty-eight right-handed native French speakers volunteered to this study (mean age = 24.02 years +/- 4.46; sex ratio = 13 males / 35 females), obeying the same criteria as in Experiment 1.

Materials

We selected a new list of 80 pronounceable pseudo-words using the Lexique toolbox (http://www.lexique.org) [4], with a number of letters ranging from 4 to 8 (mean=6.075), and a mean trigram frequency ranging from 121.5 to 2932.86 (mean=996,21). Number of letters and trigram frequency did not differ between pseudo-words and target words (p values of respective t-tests = 0.7 and 0.4). Note that a trigram frequency difference between target words and pseudo-words was present in the material used in Experiment 1 (mean trigram frequency = 1486 for pseudo-words and 1124 in target words; t-test p value = 0.04). A total number of 640 trials was presented to each participant.

Procedure and design

Procedure and design were similar to those of Experiment 1, except for the following differences. W1 were presented during 700ms, increasing the W1-W2 SOA as compared with Experiment 1 (900 ms vs 500 ms in Experiment 1). Polysemous words (W2) were presented for 33 ms both in masked and unmasked conditions, with a shorter W2-W3 SOA (100 ms vs 116 ms) in the masked condition. No fixation cross was presented before W1 and W2. We used 3 levels of masking in 3 distinct groups of 16 subjects: a first group was tested with a pre-mask duration of 33ms and a post-mask duration of 67ms; a second group was tested with no pre-mask and with a post-mask duration of 67ms; and a third group was tested with no pre-mask and with a post-mask durations of 16ms. The criterion guiding this progressive weakening of the masking procedure was the ability to identify a significant RT difference between *Icg* and *Init* conditions. This comparison is the only one assessing specifically the existence of masked W2 semantic processing, given that *Cg* trials also include a conscious semantic prime (W2-Tgt but also W1-Tgt). Moreover, in order to better circumvent automatic associations between stimulus and response codes (Abrams and Greenwald 2000; Naccache and Dehaene 2001) we used the same list of W2 for trials ending with a target word and for those ending with a pseudo-word (PW) target. Finally, we equated the proportions of trials ending with a target word and of trials ending with a PW (in comparison, PW trials proportion = 0.25 in Experiment 1). A pause was proposed every 80 trials.

2.2.2. Statistics

Multifactorial analysis of variance (ANOVA) were computed on median reaction times (RT) and on error rates. For individual analysis, we used a linear model (Wilkinson and Rogers 1973). All statistical analyses were computed using R 2.12.2 (Team 2011).

2.2.3. Results

Subjective reports about intra-trial semantic links

The vast majority of subjects (47/48; 98%) reported the presence of intra-trials semantic links between words. No subject spontaneously reported the systematic polysemous attribute of W2, and eight subjects (8/48; 17%) spontaneously reported between 1 to 3 polysemous words. Seven out of these 8 subjects ran the unmasked block in the second half of the experiment (χ^2=5.4, p=0.02). Once informed about W2 status, twenty-five subjects (25/48, 52%) were able to report one to three polysemous words. Fifteen out of these 25 subjects ran the unmasked block in the second half of the experiment (χ^2=2.09, p=0.15). As in Experiment 1, these two subjective reports findings suggest a possible memory effect specific to consciously perceived W2 stimuli.

Response times

We first ran an ANOVA on median correct RTs with the following factors of interest: Masking (2 levels) x Semantic-link (3 levels). We observed a main effect of Masking (F(1,47)=62.18; p<0.001; see Figure 3a) corresponding to shorter RTs for unmasked trials (size effect = 36ms) and a main effect of Semantic-link (F(2,94)=7.29; p=0.001) with faster RTs for *Cg* trials in comparison to both *Init* (size effect = 7ms, F(1,47)=14.5; p<0.001) and *Icg* trials (size effect = 10ms, F(1,47)=25.9; p<0.001). No significant difference was observed between *Icg* and *Init* trials (F(1,47)=1.16; p=0.29). An interaction was observed between Masking and Semantic-link (F(2,94)=6.3; p=0.03). Post-hoc analyses showed that this interaction corresponded to the presence of a significant semantic priming effect for Cg trials exclusively (*Cg* versus *Init*) in the unmasked condition (size effect = 14ms, F(2,94)=13.57; p<0.001 vs size effect = 2ms, F(2,94)=2.22; p=0.8). No difference was observed between *Icg* and *Init* trials both in masked and unmasked conditions (see Figure 3a). As in Experiment 1, we failed to detect any effect of semantic-link in the masked condition, even for the weaker type of masking. No correlation was observed between masking strength (3 levels) and semantic priming for the *Cg* condition ([*Init-Cg]*/*Init* ; adjusted R^2=-0.006, p-value=0.64)

Contrarily to Experiment 1, - and in accordance with our expectations -, no interaction was found between block order (masked or unmasked session first) and Semantic-link in the ANOVA restricted to the unmasked condition (F(2,92)=1.05; p=0.35). No other effect was found significant.

Interestingly, we discovered an unpredicted effect of response-code (hand used to answer “word” for targets) in the masked condition. We ran an ANOVA with Semantic-link (3) x Block-order (2) x Masking (2) x Response-code (2). In agreement with the preceding ANOVA, we found a main effect of masking (F(1,44)=65.88; p<0.001), a main effect of Semantic-link (F(2,88)=7.69; p<0.001), and an interaction between these two factors (F(2,88) value=6.68; p=0.002). Moreover, we discovered an interaction between Response-code and Semantic-link (F(2,88)=3.9; p=0.02), as well as a triple interaction between Masking, Response-code and Semantic-link (F(2,88)=3.95; p=0.02) (See Figure 3b). The same ANOVA restricted to subjects instructed to answer “word” with their right hand revealed a main effect of Semantic-link (F(2,44)=14.23; p<0.001) without interaction between Semantic-link and Masking ((F(2,44)=0.46; p=0.63). In sharp contrast, subjects instructed to answer “word” with their left hand did not show a significant main effect of Semantic-link (F(2,44)=1.23; p=0.3), but an interaction between Semantic-link and Masking factors

(F(2,44)=8.53; p<0.001). In other words the response-code did not matter for the unmasked condition, but only subjects instructed to answer "word" with their right hand showed a priming effect in the masked condition. Moreover, this masked priming effect was restricted to *Cg* trials (restricted ANOVA for *Cg* vs *Init* (F(1,23)=13.11; p=0.001) and for *Icg* vs *Init* (F(1,23)=0; p=0.99).

Error rates

Overall mean accuracy reached 96.92%. The ANOVA analysis crossing: Masking (2 levels) x Semantic-link (3 levels) revealed a main effect of Semantic-link (F(2,94)= 4.79; p=0.01), corresponding to a better accuracy for *Cg* trials (97.5% vs 96.8% for *Icg and* 96.5% for *Init* trials). No other effect was found significant (p values > 0.48). The ANOVA crossing: Semantic-link (3) x Block-order (2) x Masking (2) x Response-code (2) only revealed a main Semantic-link effect (F(2,88)= 4.81; p=0.01).

Masked words visibility

As in Experiment 1, the visibility of masked words was assessed with both subjective and objective measures (d'). No evidence of conscious perception of masked words was observed in any of the 3 groups of masking. Individual d' distributions were not distinct from a null distribution (mean= 0.02; CI.=[-0.5 0.9], t-test p value against a zero-centered distribution = 0.56). Linear regressions did not show a significant correlation between masked W2 priming (*Init*-*Cg*) and d' (R2=-0.013 p=0.52). However, for the "right-hand for words" sub-group only, the interpolated priming for a null d' revealed a significant priming effect (p= 0.002). No correlation was found between masked W2 priming (*Init*-*Cg*) and d' (R2= -0.03; p=0.6) suggesting that the observed priming effect was not dependent of the masked prime visibility.

Correlation analyses of masked priming effects

In order to probe masked priming effect for incongruent trials (Icg versus Init) with more sensitivity than the group-level analysis, we performed a correlation analysis between congruent and incongruent priming effects calculated at the individual level. We found a significant positive linear correlation between *Cg* semantic priming ([*Init*-*Cg*]/*Init*) and *Icg* semantic priming ([*Init*-*Icg*]/*Init*) both in masked and unmasked conditions, with a bias toward *Cg* priming as evidenced by significant estimated slope of 0.52+/- 0.13 (p< 0.001) for unmasked and 0.25 +/- 0.12 (p=0.04) for masked trials. Moreover we found and a negative estimated intercept for unmasked trials (-0.02 +/- 0.006, p=0.004). When restricting the *Icg* priming analysis to subjects showing a significant masked *Cg* priming, we observed a significant activation of the incongruent representation (Icg (581ms) vs Init (589ms); p= 0.04). Interestingly, the same analysis performed on unmasked trials did not recover a significant incongruent priming effect. This last finding suggests that incongruent semantic representations of polysemous W2 were more effectively suppressed or inhibited during the conscious condition than during the unconscious one.

2.2.4. Synthesis

In Experiment 2, the pattern of results obtained for consciously visible polysemous primes was very similar to the one reported in Marcel’s seminal study: semantic priming was restricted to the contextualized meaning of polysemous primes, whereas no priming was observed for the alternate meaning probed in the *Icg* condition. For the masked condition, the results were more complex.

First, unconscious semantic priming was present exclusively when subjects categorized target stimuli as being words with their right hand. Note that most previous LDT studies, - using conscious or subliminal prime words -, systematically used this response code without probing the impact of response code on priming effects. To our knowledge, - and in close agreement with our own findings for unmasked visible primes -, a single paper reported similar semantic priming effects with both response codes for unmasked visible words (Weems and Zaidel 2005). Note this “right-hand for words” response code was most probably used by Marcel in his own set of experiments, even if the information is not fully explicit in his article.

Second and most importantly, we could find an unconscious semantic priming effect in Experiment 2, but it was restricted to the contextualized meaning (*Cg* condition), with no behavioral evidence of automatic processing of the two semantic representations of polysemous words. This result clearly contradicts Marcel’s result and suggest that processing of masked words is not fully automatic but sensitive to top-down factors such as the conscious context setting.

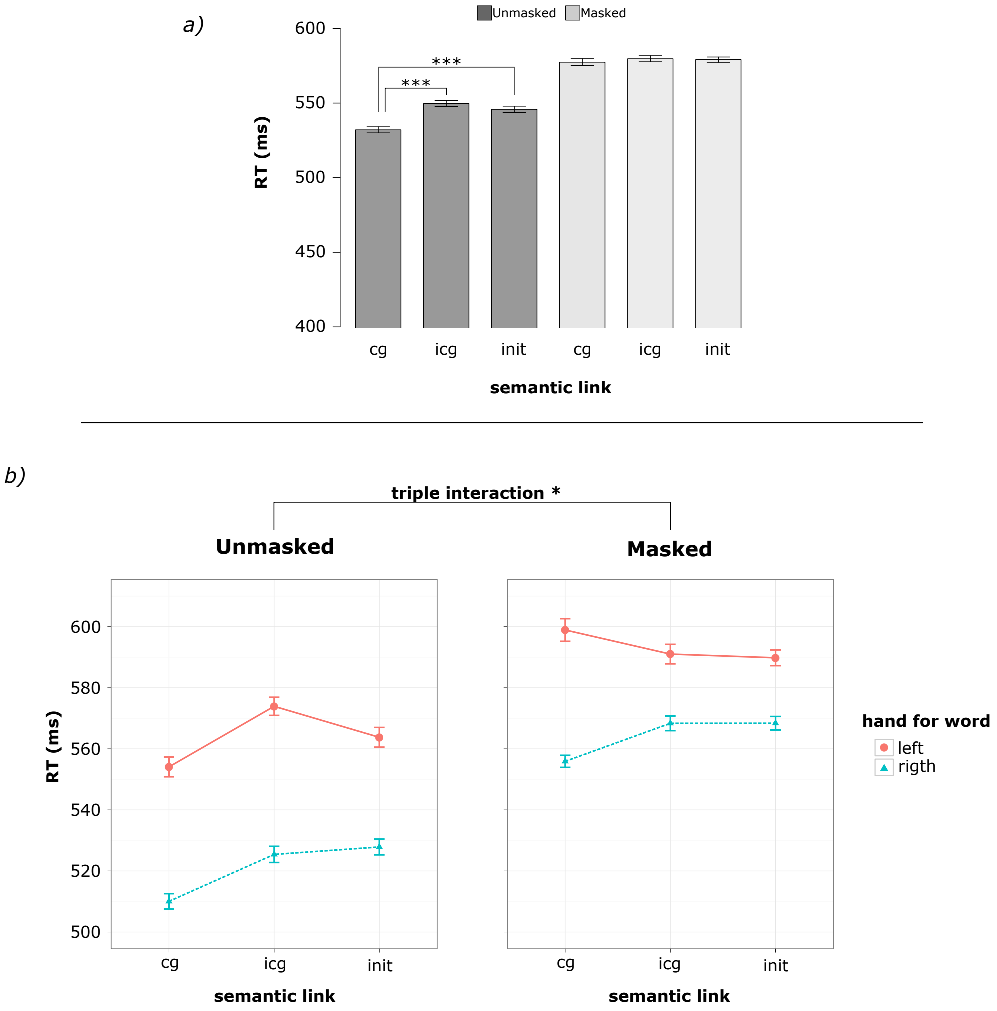


Figure 3. Semantic priming in Experiment 2

*(a) Median correct RTs for each condition (Cg=Congruent, Icg= Incongruent, Init=Initial) in masked and unmasked blocks revealed a semantic-link effect in unmasked block only, corresponding to shorter RTs for the contextualized meaning of the polysemous W2 (Cg). Bars indicate standard errors of mean ; *** = p<0.001; ** = p<0.01; * = p<0.05*

(b) Post-hoc analyses revealed a priming effect in the masked block dependent on the response-code: subjects instructed with the “right hand for words” response-code showed a priming effect limited to the contextualized meaning of the polysemous W2 (Cg), whereas no effect was observed for the reverse instruction.

2.3. Experiment 3

Experiment 3 was designed in order to better understand the origin of contextual (congruent priming effect) and task instruction (response code) influences on the fate of masked words.

To do so, we focused exclusively on masked trials, and varied response code as a within-subject factor (while it was previously a between-subjects factor). We also added the ‘Separate’ condition (word1-word3 link) as in Experiment 1 to better disentangle between W1 and masked W2 priming effects. Note that our design allowed us to test the respective weighs of W1 and W2 priming effects contrarily to Experiment 1 in which these 2 factors were not orthogonal. We designed an ERP version of this task in order to test two distinct scenarios.
According to a first hypothesis, masked words would always elicit an internal semantic priming effects localized in the left hemisphere. Therefore, assuming a more direct link between the left hemisphere and the right hand, this effect would be mostly visible behaviorally when the ‘right hand for word’ code is used. Under such a hypothesis ERPs could reveal this systematic left-hemisphere priming effect irrespectively of the current response code. Alternatively, one may imagine that response code influenced the task strategy set by subjects. For instance, one could imagine that the target assigned to the right dominant hand drives the processing strategy. Thus when words had to be answered with the right hand, a semantic strategy may be emphasized (“looking for real words”), whereas a lexical strategy may be facilitated when pseudo-words had to be detected by pressing the right hand (“looking for pseudo-words”). Clearly, ERPs should be able to compare these two explanatory models of our behavioral data. Finally, we decided to add the Sep condition in which Target words are semantically related to W1 and not to W2. Indeed, the Cg priming effect observed in Experiment 2 may be caused both by unmasked W1 and by masked W2 given that these two words are, - by transitivity -, semantically related to target words. Note however that our masked priming effect is not easily explainable in terms of conscious W1 priming given the absence of such a W1 priming effect in Sep condition in Experiment 1, and given the absence of Cg priming effect for “left-hand for words” response-code.

2.3.1. Material and Methods

Participants

Sixteen right-handed native French speakers volunteered to this study (mean age = 24.5 years +/- 4.59; sex ratio = 8 males / 8 females). They had no neurological or psychiatric history, were free of any medication and had normal or corrected to normal vision. All participants gave written informed consent, and the experiment was approved by the Ethical Committee of the Pitié-Salpêtrière Hospital, APHP (n°80-10).

Materials

We used the same material as in the Experiment 2. However in order to disentangle the effect of masked priming observed in Experiment 2 we added the *Separate* condition.

Procedure and design

We used the light masking condition described in Experiment 2 (W2 presented for 33ms with no pre-mask and followed by a 16ms post-mask), and inverted the response-code at the middle of the experiment (response-code order was balanced across subjects). In order to avoid a too long experiment we only used masked trials.

EEG recording and processing

EEG was sampled at 250 Hz with a 256-electrode geodesic sensor net connected to a high impendence amplifier (EGI, Oregon, USA) referenced to the vertex. Impedances were controlled inferior to 100 kΩ. Data were filtered from 0.5 Hz to 30 Hz. Trials were segmented from -300ms to 900ms relative to the onset of the target stimulus (word/peudo-word).

Trials with more than 10 channels containing voltage-exceeding ±100µV were rejected. For the remaining trials, bad channels were interpolated from contiguous electrodes. Remaining trials were averaged, digitally transformed to an average reference, and corrected for baseline over a 200ms window spanning from -300ms to -100ms before Tgt onset in order to avoid W2 P1/N1 complex time window. All these pre-processing stages were performed in Fieldtrip (Oostenveld, Fries et al. 2011).

2.3.2. Statistics

Behavior

See Experiment 2.

ERPs

We used a combination of 4 approaches.

We first computed a non-parametric statistic implemented in Fieldtrip described fully in (Maris and Oostenveld 2007). Briefly, this procedure first compares spatiotemporal data-points across conditions using a t-tests. The single-subject ERP averages elicited by each stimulus type were compared using one-tailed dependent samples t-tests. Although this t-test step is parametric, FieldTrip employs a secondary nonparametric clustering method to address the multiple comparisons problem. Specifically, t-values of adjacent spatiotemporal points whose p-values were < .05 were clustered together by summating their t-values, and the largest such cluster was retained. A minimum of two neighboring electrodes had to pass this threshold to form a cluster. This entire procedure, that is, calculation of t-values at each spatiotemporal point followed by clustering of adjacent t-values, was then repeated 1000 times, with recombination and randomized resampling of the ERP data before each repetition. This Monte Carlo method generated a nonparametric estimate of the p-value representing the statistical significance of the originally identified cluster. This approach provides increased power relative to other corrections for multiple comparisons such as Bonferroni correction and False- Discovery Rate.

Second, we also computed a triple-threshold parametric method as reported in our previous studies (Bekinschtein, Dehaene et al. 2009 ; Faugeras, Rohaut et al. 2011 ; Faugeras, Rohaut et al. 2012 ; Rohaut, Faugeras et al. 2014). This method consists in sample-by-sample paired t-tests with a triple criterion: t-test p-value was categorized in three levels (non-significant, $0.01 \leq p < 0.05$ or < 0.01), for a minimal duration of 5 consecutive samples (20ms), at least on 10 electrodes.

Third, we also used a region of interest (ROI) approach by computing sample-by-sample paired t-tests on the mean signal averaged across the contiguous electrodes of 3 spatial ROIs (two posterior lateral ROIs and an anterior mesial ROI). Note that this method is circular when applied to a preselected region in which an effect has been detected by the mean of one of the two previous methods (see the ‘double dipping’ issue raised by (Kriegeskorte, Simmons et al. 2009), but it is useful to better capture the overall differences of time-courses across conditions.

Finally, we used a spatial regression method in which we probed the resemblance of time-courses of ERPs with vectors defining topography of interest (Pegado, Bekinschtein et al. 2010 ; Faugeras, Rohaut et al. 2012 ; Rohaut, Faugeras et al. 2014).

2.3.3. Results

Behavior

All subjects reported the occasional presence of intra-trials semantic links between W1 and Target.

Reaction times

We first ran the following ANOVA: Response-code (2) x Semantic-link (4) x Block-order (2), with subject declared as a random factor. A trend toward a main effect of Semantic-link was observed (F(3,42)=2.34;p=0.09), while no other main effect or interaction was found significant (all p values > 0.2). We then assessed separately priming effects of W1 and W2 by declaring the following ANOVA: Response-code (2) x W1-Tgt semantic priming (2) x W2-Tgt semantic priming (2). A weak effect of W1-Tgt priming was present (529ms vs 534ms; F(1,15)=4.4; p=0.053), while no effect of W2-Tgt priming was found significant (F(1,15)=0.7; p=0.4). None of the interactions reached statistical significance (all p-values >0.16).

Error rates

Overall mean accuracy reached 96.99%. Both ANOVAs did not reveal any significant effect (all p-values > 0.25).

Masked words visibility

In spite of the absence of subjective report of prime visibility, the distribution of individual d' values was significantly distinct from a null distribution (mean d'= 0.18; CI= [0.05 0.31], t-test p-value against a zero centered distribution = 0.01). Linear regressions analyses did not show any correlation between d' and priming index in *Cg* trials ([*Sep – Cg*] / *Sep*, R2= -0.03;

p=0.5), the Y-axis intercept (corresponding to the estimated priming effect for a null visibility) was not different from zero (p=0.84).

ERPs

We first computed the lexical contrast [Peudo-words – Words] in order to define the temporal window(s) of interest for lexico-semantic effects. A massive N400 effect was observed on the central region, followed by a late positive component (LPC or P600). These effects were significant with both cluster-based-permutation and triple-threshold statistic methods, and spanned respectively from 200-650ms for the N400, and from 640-880ms for the LPC/P600 (see Figure 4, panel a: PW-W).

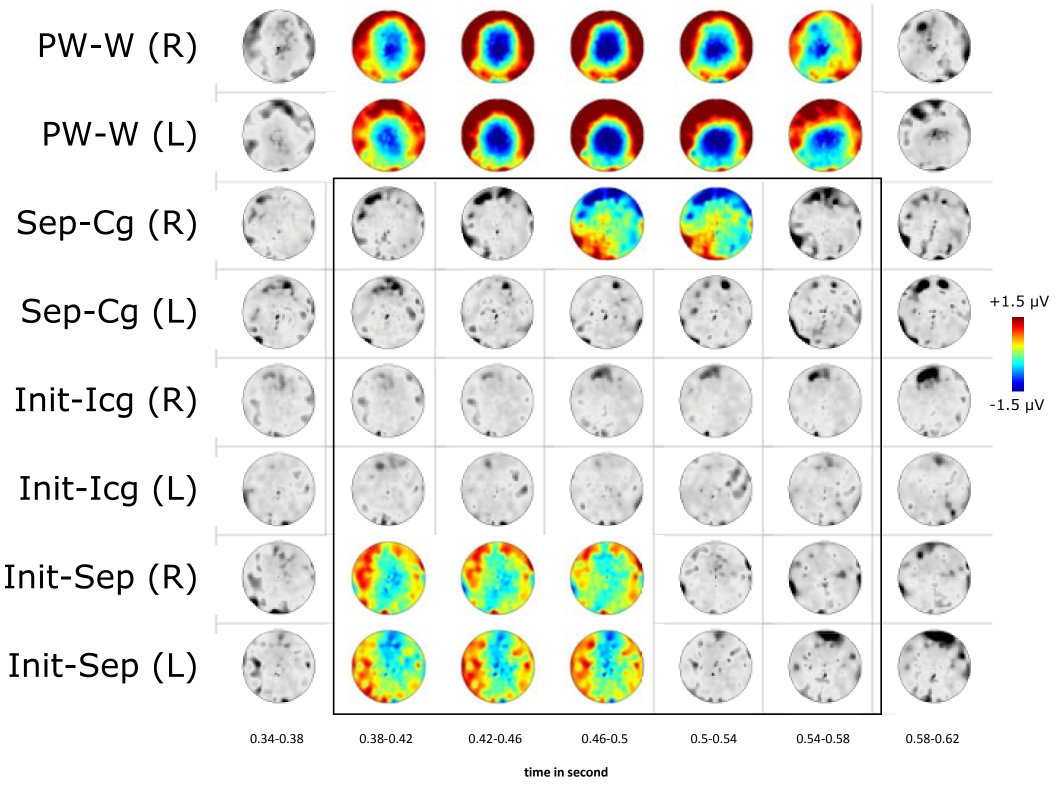
We then probed each of our contrasts of interest regarding W2 semantic priming effects in these two lexico-semantic time-windows as defined with the most stringent method (cluster-based permutations statistics).

In order to isolate neural correlates of the contextualized semantic priming effect of polysemous W2 on Tgt, we computed the [Separation – Congruent] contrast. This analysis revealed a significant posterior left-lateralized positivity during the N400 window (480-530ms; triple-threshold procedure with $p \leq 0.05$). As observed in the behavioral results of Experiment 2, this effect was dependent on response-code: it was significant for ‘right-hand for words’ code, and absent for ‘left-hand for words’ code (see Figure 4, third and fourth rows). We confirmed this result by running an ANOVA with: Response-code (2) X Semantic-link (2) with subject as a random factor, on voltages averaged in the left posterior ROI over the 480-530ms time-window. A significant interaction was found between Semantic-link and Response-code (F(1,15)=4.75; p=0.045). Restricted contrasts confirmed that this effect was observed for ‘right-hand for words’ code (F(1,15)=7.9; p=0.01), while no effect was observed for the other code ((F(1,15)=0.33; p=0.57). In the late LPC/P600 window, we observed an anterior positivity in both response codes conditions (see Figure 5, 3rd and 4th rows).

In order to isolate the neural correlates of the non-contextualized semantic priming effect of polysemous W2 on Tgt, we computed the [Initial – Incongruent] contrast. This analysis revealed no effect using each of the 3 first statistical methods (all p-values >0.2) in the N400 time-window. However the regression approach computed with the topography of the peak of W2-Tgt semantic priming effect ([Sep-Cg]) revealed the existence of a significant activation of the non contextualized meaning of W2 during the N400 time-window, exclusively for ‘right-hand for words’ response code (see Supplementary Figure 1). In the late LPC/P600 window, a sustained anterior negativity, - similar to the one present in the LPC/P600 topography -, was present in both response codes conditions (see Figure 5, 5th and 6th rows) using the triple-threshold method. The ANOVA computed on the anterior ROI confirmed this pattern by showing a main effect of Semantic-link (F(1,15)=8.2; p=0.012), with no significant effect of the response-code factor and of the interaction between these two factors (both p-values >0.5).

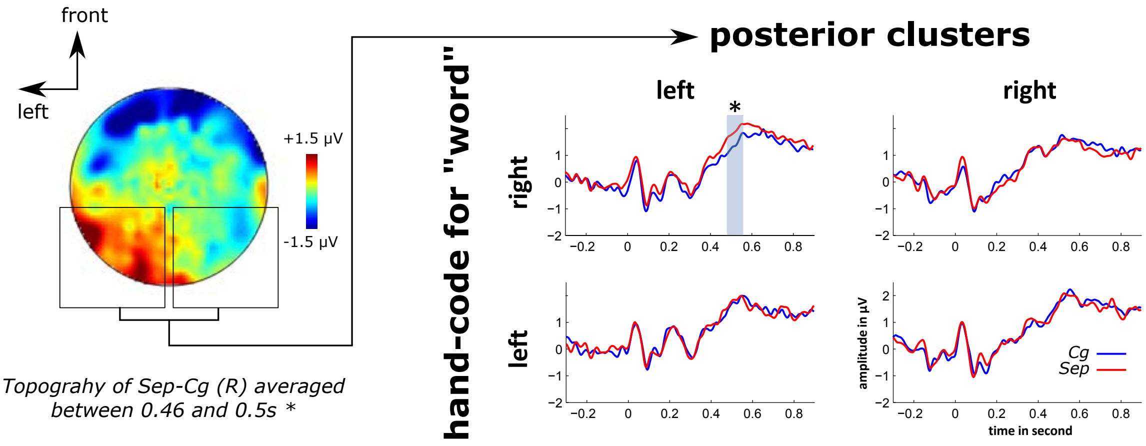
Finally, we performed 3 ANOVAs similar to the one run in Experiment 1, in order to assess orthogonally W1 and W2 priming effects on target words : W1-priming (2) X W2-priming (2) X Response-code (2) with subject declared as a random factor, on voltages averaged across the N400 time-windows for left and right posterior ROIs separately, and averaged across the LPC/P600 time-window for the anterior midline ROI (see Figure 7). In the left posterior ROI, we observed a marginal N400 effect of W1-priming (F(1,15)=4.24; p=0.06), as well as a significant effect of W2-priming (F(1,15)=5.54; p=0.03), with no main effect of response-code (F(1,15)=1.52; p=0.24). Most crucially, an interaction between W2-priming and response-code was present (F(1,15)=6; p=0.03), corresponding to a W2-priming effect exclusively for ‘right-hand for words’ condition (F(1,15)=8; p=0.01). The same analysis performed on the right posterior ROI did not reveal any significant effect. For the anterior midline ROI this ANOVA revealed a main effect of W2-priming (F(1,15)=5.39; p=0.03) which did not interact with response-code (p=0.9). All other effects were not significant.

a)



Topographies of contrasts of interest in the N400 window

b)



*Topograhy of Sep-Cg (R) averaged between 0.46 and 0.5s **

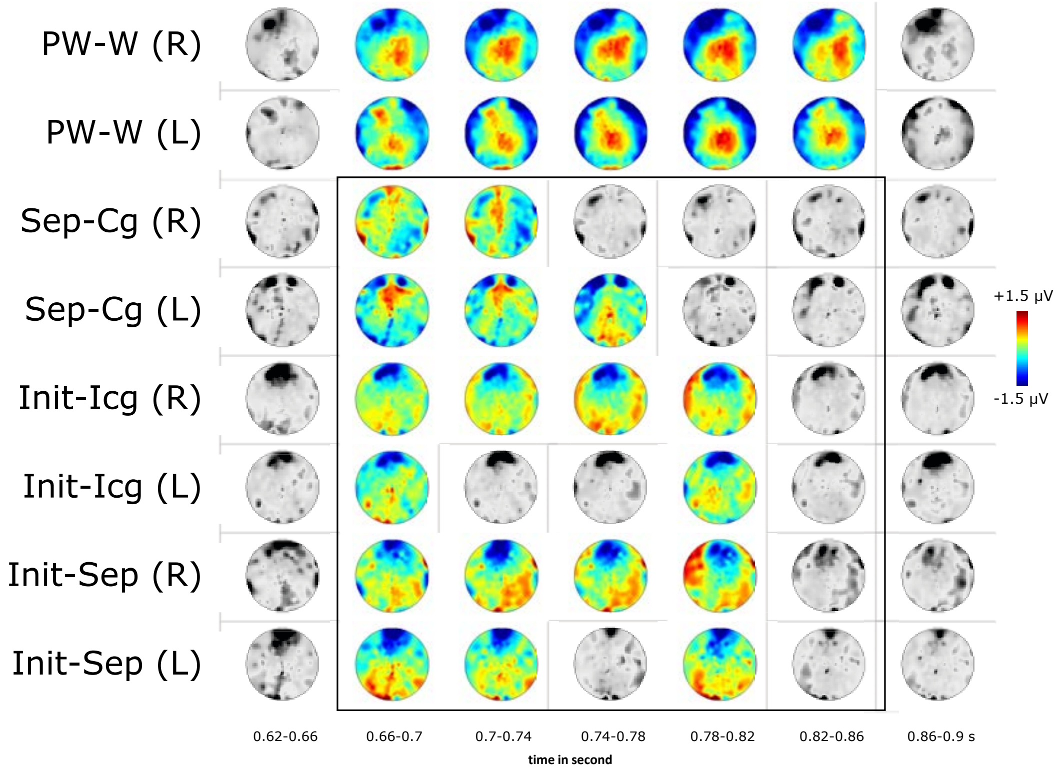
ERPs averaged across clusters for the (Sep-Cg) contrast

Figure 4. Semantic priming ERP effect within the N400 time-window

(a) ERP effects occurring within the general N400 time-window are reported. The N400 time-window was defined by the contrast Pseudo-word (PW) –Word (W). Statistical effects using a non-parametric cluster-based approach for the PW-W contrast (first two rows), and a parametric approach based on a sample-by-sample paired t-test with a triple criterion are plotted in color-map. Non-significant topographies are plotted in black & white. Cg=Congruent, Icg= Incongruent, Init=Initial, Sep=Separate;R=”right-hand for words” code; L=”left-hand for words” code. The [Sep-Cg] contrast revealed a left-lateralized

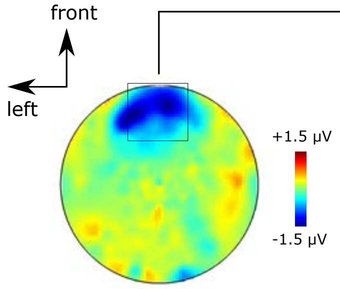
*priming effect of the contextualized meaning of masked polysemous words for the ‘right-hand for words’ code. (b) The ROI approach showed the time-course of the left lateralized priming effect of the contextualized meaning of masked polysemous words for the ‘right-hand for words’ code. Bars indicate standard errors of mean; * = p<0.05*

a)

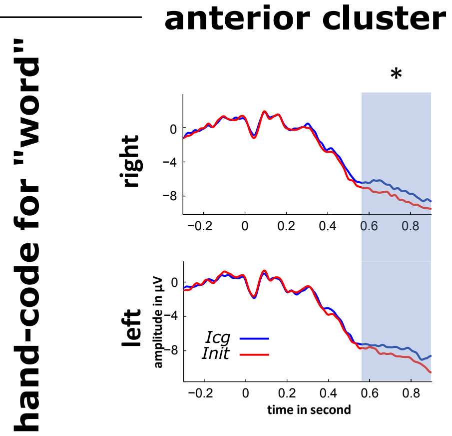


Topographies of contrasts of interest in the LPC window

b)



*Topograhy of Init-Icg (RL) averaged between 0.58 and 0.9s **



ERPs averaged in anterior cluster for the (Init-Icg) contrast

Figure 5. Semantic priming ERP effect within the LPC/P600 time-window

(a) ERP effects occurring within the general LPC/P600 time-window are reported. The LPC/P600 time-window was defined by the contrast Pseudo-word (PW) –Word (W). Statistical effects using a non-parametric cluster-based approach for the PW-W contrast (first two rows), and a parametric approach based on a sample-by-sample paired t-test with a triple criterion are plotted in color-map. Non-significant topographies are plotted in black & white. Cg=Congruent, Icg= Incongruent, Init=Initial, Sep=Separate; R=”right-hand for words” code; L=”left-hand for words” code. A significant effect was observed in all conditions as compared to Sep or Init. (b) The ROI approach showed the time course of the anterior negativity observed in [Init-Icg] contrast, which did not to depend on the response-code. *** *= p<0.05*

2.3.4. Synthesis

We did not obtain behavioral priming effects in Experiment 3 which used only masked priming trials. In spite of this negative finding, ERPs revealed results in agreement with our previous behavioral findings on the impact of response-code on contextualized-W2 target masked priming effects. The left-lateralized effect occurring during the N400 window was exclusively present for ‘right-hand for words’ response-code. Moreover, we detected a similar but weaker effect only with the topography regression analysis for the non-contextualized meaning of polysemous W2. These two findings suggest that both meanings of masked polysemous words were activated, although the contextualized meaning was more activated than the non-contextualized one. Finally, the late processing of target words (LPC/P600 window) revealed an original pattern: an anterior negativity was present in all conditions in which targets were semantically primed, either by W1 and/or by W2. This last effect was not dependent on response-code.

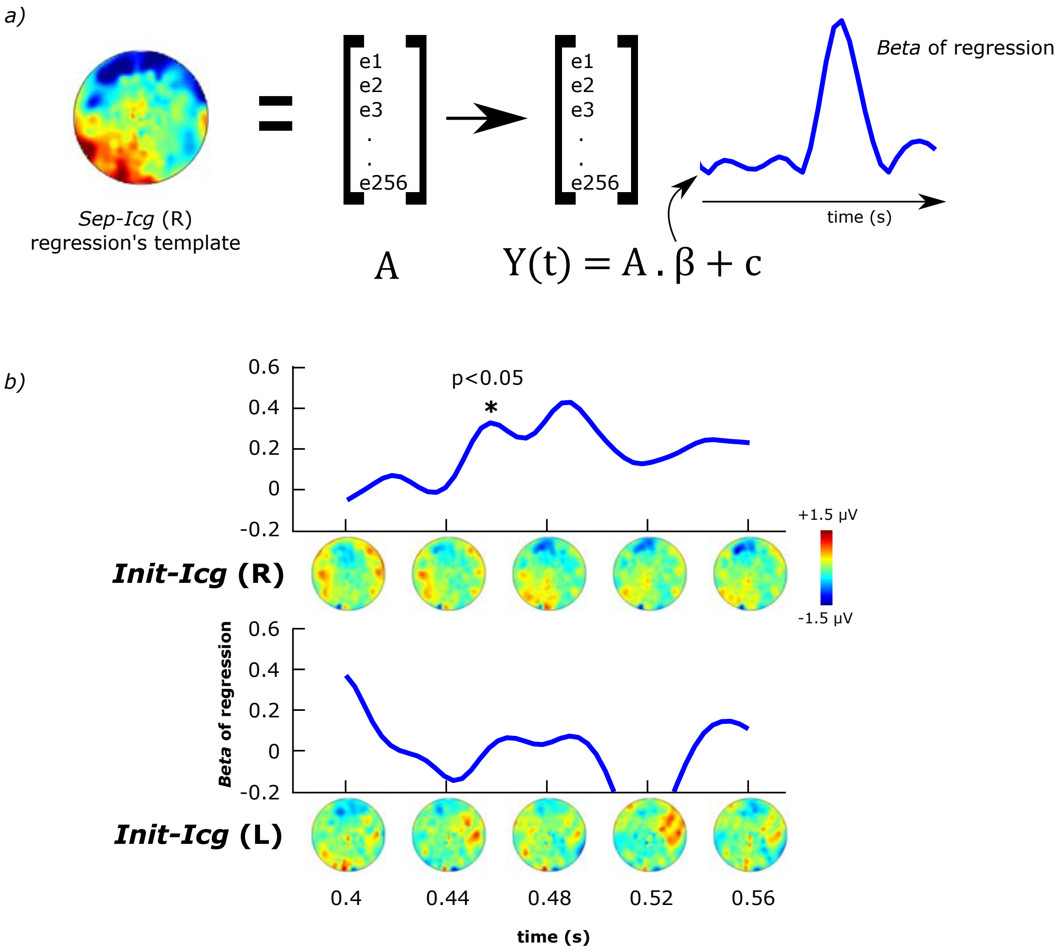
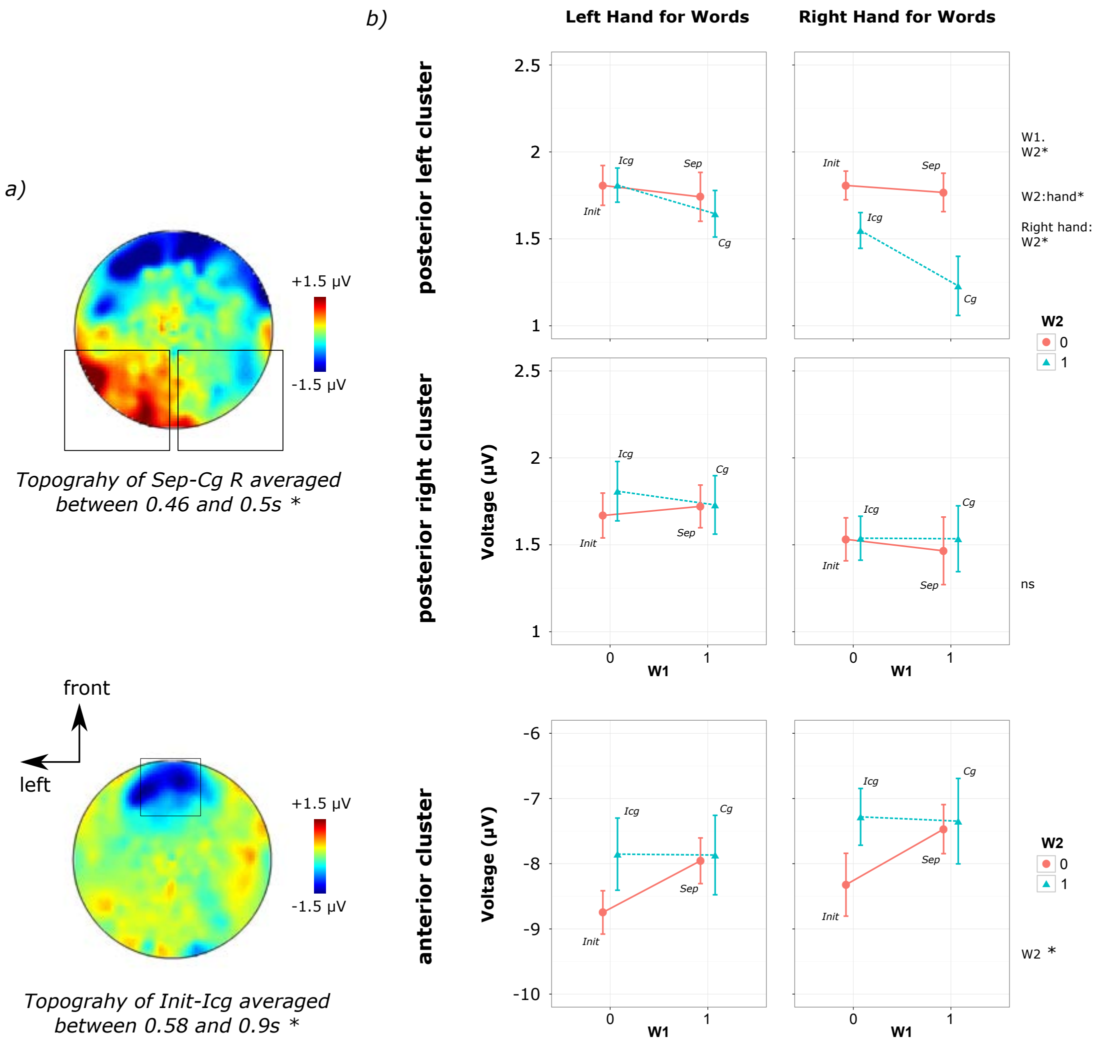


Figure 6. A correlate of unconscious semantic processing of the non-contextualized meaning of polysemous words

Using a regression approach on canonical topography of the [Sep-Cg] effect (see (a) and text), we detected a significant semantic priming effect for non-contextualized meanings of W2 during the N400 window, exclusively for trials answered with the 'right-hand for words' code.



*Topograhy of Sep-Cg R averaged between 0.46 and 0.5s **

*Topograhy of Init-Icg averaged between 0.58 and 0.9s **

* p<0.05 on >10 electrodes and >20ms

Figure 7. ERP correlates of W1 and W2 semantic priming effects

(a) Topographies of masked W2 contextual priming effect in the early window for ‘right-hand for words’ (N400 window), and of masked W2 non-contextualized priming effect in the late window (LPC/P600 window) of target processing. (b) Correspondent ROIs voltages: while the W2 early effect was exclusively observed for ‘right-hand for words’ code, the late effect was observed for all conditions including a semantic link between target words and W1 and W2 words, irrespective of response-code.

3. Discussion

In this work, we revisited the seminal experiments of Marcel on the unconscious processing of polysemous words using: i) more stringent methods to present masked stimuli and to assess visibility as well as semantic processing, and ii) a combination of behavioural and ERPs measures. Our results can be summarized in four points leading to a convergent conclusion.

First, concerning consciously visible polysemous prime words we replicated the original result reported by Meyer and Schvaneveldt (Meyer and Schvaneveldt 1971) and by Marcel (1980): only the contextualized meaning of consciously perceived polysemous words primed target processing. However, we observed that this phenomenon could disappear under conditions of slowing down of RTs suggestive of cognitive fatigue.

Second and most importantly, concerning masked polysemous prime words our results diverged totally from Marcel’s findings. Unconscious semantic processing of masked words was observed both in behaviour and in ERPs data but it was extremely sensitive to the conscious context defined by W1.

Third, this sensitivity of unconscious semantic processing was also found in relation to the response-code used to answer targets.

Fourth, we detected an ERP correlate of semantic processing of both meanings of the masked word in the late window of conscious processing of target words.

Restriction of polysemy: consciousness or cognitive control?

The partial replication of Marcel’s result for consciously perceptible prime words may be interpreted in two distinct ways.

One interpretation may posit that restriction of polysemy according to the context requires the contribution of executive control in addition to conscious perception. When subjects are conscious of W2 but tired, - as we hypothesized for those who performed unmasked blocks during the second half of the experiment and with longer RTs -, they may lose this restriction of polysemy due to insufficient cognitive control resources during this rapid-serial-visual-presentation task. Indeed, several studies reported the implication of prefrontal cortex areas in the implementation of contextual selection processes over ambiguous or polysemous verbal semantic representations (Thompson-Schill, D'Esposito et al. 1997; Thompson-Schill, D'Esposito et al. 1999; Ihara, Hayakawa et al. 2007). A more causal link between the left inferior frontal gyrus (LIFG) and this selection process of contextual semantic representations of polysemous words has been provided by patients studies showing that it is impaired when a focal brain lesion affects this precise area (Hagoort 1993; Swaab, Brown et al. 2003). Recently, a trans-cranial direct current stimulation over this area has been reported as enhancing this contextual selection process in the case of ambiguous words (Ihara, Mimura et al. 2015). Interestingly, previous studies reported such a similar behavioural effect as the one we observed for short SOAs (<300ms versus 500ms in our case) (Swinney, Onifer et al. 1979; Onifer and Swinney 1981) but not for longer SOAs as the ones used in our study.

Alternatively, one may imagine that under conditions of fatigue, subjects would not have use the contextual word (W1) efficiently, and therefore would not have defined a strong semantic context. If so, then the semantic priming of both meanings of unmasked words would not reflect the loss of polysemy restriction, but rather the mere absence of context. At this stage we cannot decide between these two hypotheses. However, this result stresses that future experiments using this triple-word paradigm must include objective evidence of W1 processing. For instance the use of ERP correlates of early (P1/N1) and late (P300/N400) stages of W1 processing may be necessary to provide a univocal interpretation of the absence of polysemy restriction effect.

Restriction of polysemy for unconscious prime words

In experiments 2 and 3 we collected behavioural and ERP evidence demonstrating a strict restriction of unconscious semantic processing of masked polysemous words according to the conscious context. A behavioural priming effect (experiment 2) as a N400 effect (experiment 3) were observed in response to congruent trials and not to incongruent trials. Per se, these two results establish the existence of top-down contextual control over non conscious verbal semantic representations. Resolution of lexical ambiguity in the case of consciously visible words is still a subject of theoretical discussion between 4 types of models (Simpson 1984): context-dependent, ordered-access, exhaustive access and hybrid models In our case, the absence of behavioural effect in the incongruent condition at short SOAs (100ms) suggests either a context-dependent model even for unconsciously perceived words, or a very early inhibition process. Eckstein and colleagues probed both unmasked and masked priming effects across SOAs ranging from 100ms to 1500ms, and reported a faster subliminal selection of dominant versus rare meanings of polysemous words for masked primes (Eckstein, Kubat et al. 2011). Our study adds a notable result to this previous report: in our case, this semantic selection process was not inherent to W2 meanings frequencies, but was driven by the conscious context defined by W1, and occurred among the two meanings of polysemous words W2, irrespectively of their relative strength. This indicates that the modulation was not intrinsic to W2 but contextualized by W1. The absence of behavioural effect in ERP experiment 3 constitutes a limitation of our results. However, note that only masked primes were used in this experiment, preventing thus the optimal focusing of exogenous and endogenous temporal attention to the critical onset of masked words (Naccache, Blandin et al. 2002; Kiefer and Brendel 2006). Moreover, the similarity of response-code impact on both behaviour and ERP effects (see below) strongly suggests that these two experiments tap onto the common unconscious semantic processing of masked polysemous words. This result clearly contradicts the original finding of Marcel who used less rigorous methods of prime visibility assessment and who used much longer SOAs than we did. A possible explanation of the discrepancy between Marcel’s results and our own results could be found in the following scenario based on 3 premises: i) while most masked priming effects show a fast decay with no residual effect after few hundreds of milliseconds (Greenwald 1996; Naccache, Blandin et al. 2002), Marcel’s effects persisted with a much longer SOA of 1500ms; ii) most Marcel’s effects have been criticized due to the lack of correct assessment of the absence of conscious visibility of masked primes (Purcell, Stewart et al. 1983; Cheesman and Merikle 1984; Holender 1986) ; iii) the restriction of polysemy by context requires the context to be attended and processed (as demonstrated in our experiment 1 with a conscious polysemous priming effect when the context is not well processed). Therefore, it may well be the case that in Marcel’s experiments masked primes were consciously perceptible but with the need of some effort. In turn, this may have induced an attentional focus onto the prime stimuli, at the expense of deep and sustained semantic processing of contextual word W1. As a net result, Marcel may have measured conscious priming effects in the absence (or relative absence) or contextual setting. This scenario predicts a conscious polysemous priming effect with masked primes, and a conscious priming effect restricted to the contextualized meaning for unmasked primes. As we stated above, these comments call for a crucial control in future experiments on polysemous priming: in order to claim the absence of polysemy restriction by the context, one must provide evidence of context processing using either behavioural or functional-brain imaging evidence (e.g.: ERPs, fMRI).

Our demonstration of a similar sensitivity of conscious and unconscious processing of polysemous words to the conscious context constitutes a new step in the general description of rich and various influences on many unconscious cognitive processes. The whole notion of modularity and of automaticity seems to be breached by a collection of diverse empirical reports, and further strengthen the functional proximity of conscious and unconscious cognitive processes which are hosted by similar cortical networks as theorized in the global workspace model of consciousness (Baars 1989; Dehaene and Naccache 2001; Dehaene, Changeux et al. 2006; Naccache 2006). Interestingly, the detection of the behavioural or functional brain-imaging correlates of these conscious influences on unconscious processing may prove extremely useful in a challenging medical context. They may help determine the level of conscious awareness of patients suffering from disorders of consciousness, in whom clinical examination is very limited (Giacino, Fins, Laureys, & Schiff, 2014; Laureys, Owen, & Schiff, 2004; B Rohaut, Faugeras, & Naccache, 2013). Coleman et al. used fMRI to probe the processing of ambiguous sentences and reported the contribution of LIFG in some severely disabled patients (Coleman, Rodd et al. 2007). For instance, we recently demonstrated that an auditory N400 priming effect was present in conscious controls as well as in minimally conscious (MCS) and vegetative state (VS) groups of patients, whereas only MCS patients and conscious controls showed of LPC/P600 effect (Rohaut, Faugeras et al. 2014). The demonstration of an impact of a semantic context on the processing of polysemous words could be a solid index of conscious integration of the semantic context.

A new effect of hand-response code

The third original finding of our study consists in the strong impact of response code on unconscious priming. While this response code factor did not interact with conscious semantic priming effect, unconscious priming occurred exclusively for ‘right-hand for words’ instruction in this LDT. We may put forward two main explanations for it. On the one hand, unconscious semantic processing could be localized in a left-hemispheric processor (S Dehaene & Naccache, 2001; Schmidt, Palminteri, Lafargue, & Pessiglione, 2010), whereas conscious access to this representation would co-occur with its availability to widespread bi-hemispheric global workspace. Under such a hypothesis, conscious priming would not depend on response-code while unconscious semantic priming would only prime the left-hemispheric motor network, and subsequently translate into behaviour (RT) only when subjects had to use their right hand to categorize target stimuli as words. This hypothesis predicts that this systematic left-hemispheric semantic priming effect should be detected using ERPs in both response code conditions. In contrast, one may imagine a less parsimonious scenario in which the instruction of responding to words with the right-hand would enhance left-hemispheric language network activity, and would then strategically orient subjects to perform a “word detection” task, whereas the opposite instruction would bias them to perform “pseudo-word detection” task. Additionally, this bias would be more effective on unconscious representations. This hypothesis predicts that left-hemispheric correlate of masked words would be highly dependent on response code. ERP results of experiment 3 were clearly in favour of this second scenario. The left-hemispheric N400 effect was observed only for ‘right-hand for words’ trials. This intra-subject effect could not be explained as a correlate of right-hand motor preparation given that we contrasted trials answered with the right-hand ([Sep-Cg]), and given the absence of RT difference between these two conditions (Sep and Cg). Additional studies would be important to probe the level of metacognitive knowledge of subjects: do they voluntarily engage in such a task strategy? At least, is this process accessible to their conscious introspection? Is this effect also present on unmasked words, even if it does not translate to behaviour? As a first step in that direction, we probed (experiments 1 and 2) the reportability of unmasked W2 polysemy, which was not negligible (~10-30%).

Finally, it is noteworthy that most LDT studies are conducted with the ‘right-hand for words’ response code, without any strong justification for this consensual convention, except the finding that response code does not affect semantic priming effects of consciously visible words (Weems and Zaidel 2005). According to our results, this choice may stem from this left-hemispheric task strategy and may be more sensitive to conscious and unconscious semantic priming effects.

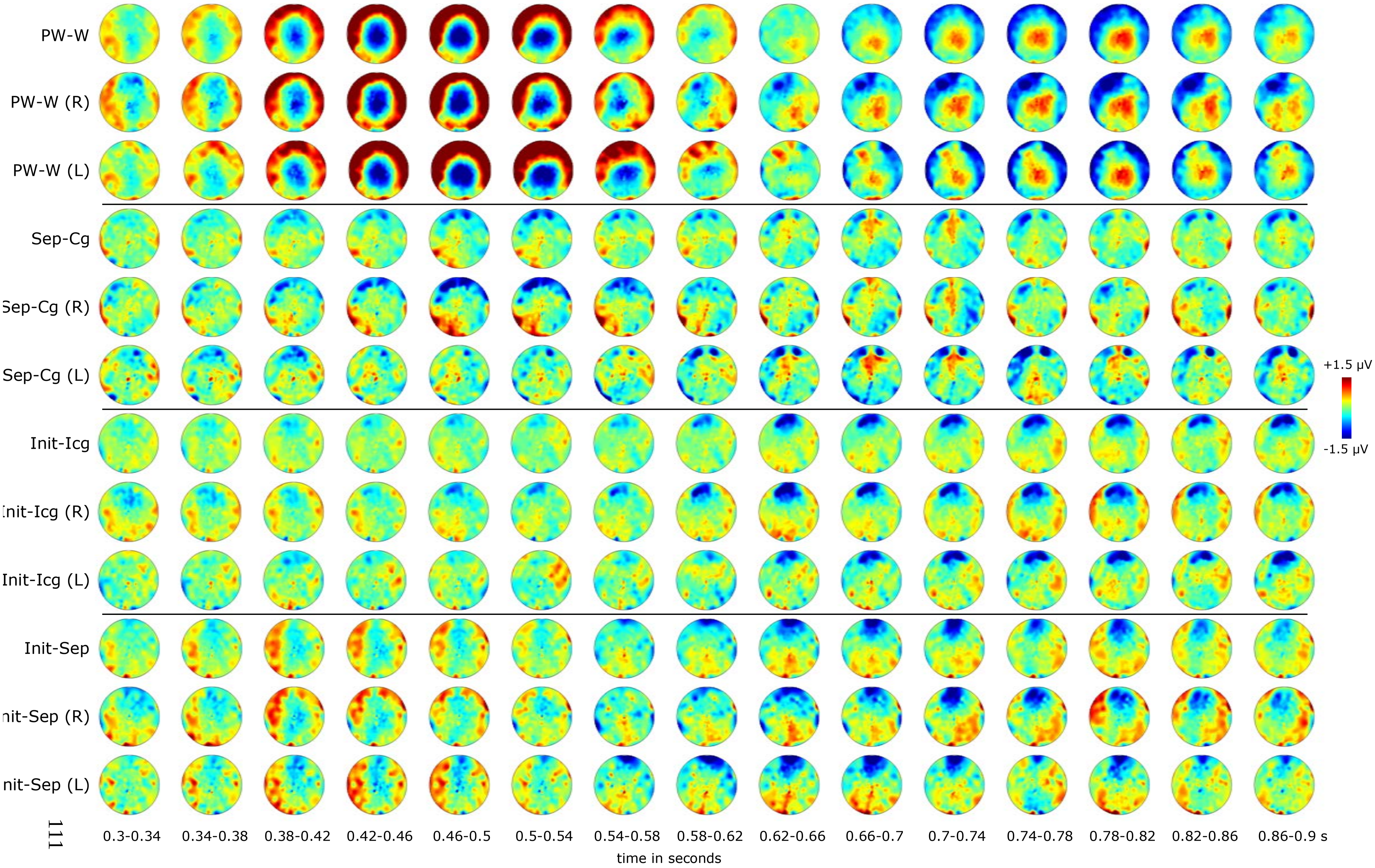
Target words acting as retro-contextual cues?

An unexpected finding of our ERP experiment is this late LPC/P600 component modulated by all forms of semantic link between targets and other words: masked or unmasked prime words (W2) or contextual words (W1). This late effect did not translate into behaviour and was not dependent on two factors manipulated in this experiment: semantic context and response-code. As we noted, this effect was not restricted to prime words and escaped these two factors which dramatically affected both behavioural and ERP priming effects. We propose that rather than being a priming effect of W1 or W2 on target words, this ERP modulation could reflect a retroactive effect: once the consciously visible target word is processed semantically, this current semantic representation could retroactively modulate all other available lexical or semantic representations of W1 and/or W2 which are still actively encoded in lexico-semantic networks. If correct, our interpretation means that a lexical pre-semantic representation of masked polysemous W2 is still active at this latency. This hypothesis is reminiscent conceptually of a recently demonstrated retro-cueing effect corresponding to an enhancement of unconscious representations after the presentation of a spatial attention cue (Sergent, Ruff et al. 2011; Sergent, Wyart et al. 2013).

We conclude by stating that the results of the present study extend the concept of flexibility and sensitivity of high-level unconscious processes to several top-down factors.

Supplementary Figure. Full time widow of all ERP contrasts of interest

Topography of contrasts of interest between 0.3 and 0.9s after the onset of target words. Cg=Congruent, Icg= Incongruent, Init=Initial, Sep=Separate
R=‘right hand for words’ code; L=‘left hand for words’ code; RL= grand average of R & L blocks



Topographies of all contrasts of interest between 0.3 and 0.9s after the target's onset

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2.3 Supplementary material

Experimental material

a) Experimental list

Context meaning 1	Context meaning 2	Polysemous word	Target meaning 1	Target meaning 2
recharge	tambour	batterie	pile	cymbale
gisement	crayon	mine	charbon	stylo
tracteur	oiseau	grue	chantier	héron
miroir	dessert	glace	vitre	sorbet
clavier	ski	moniteur	écran	guide
chirurgie	maths	opération	bistouri	division
ordinateur	rat	souris	internet	hamster
nez	chemise	bouton	acné	couture
cirque	carré	trapèze	clown	losange
niais	pichet	cruche	idiot	carafe
couette	poil	duvet	édredon	barbe
troupe	plâtre	bande	clan	entorse
paume	jardin	plante	pied	racine
montre	collège	seconde	minute	lycée
insecte	chagrin	cafard	fourmi	ennui
colis	chiffre	lettre	timbre	alphabet
alliance	musique	accord	union	guitare
tarif	trophée	prix	coût	médaille
météo	heure	temps	pluie	horloge
forêt	papier	feuille	arbre	cahier
vertèbre	océan	côte	thorax	rivage
poisson	café	bar	thon	bistrot
rhume	torrent	gorge	angine	cascade
visage	bateau	voile	masque	vent
marin	savon	mousse	navire	lessive
fève	myopie	lentilles	haricot	opticien
film	poireau	navet	western	courge
chaise	fichier	dossier	fauteuil	classeur
boue	tulipe	vase	gadoue	fleur
huître	four	moule	crabe	cake
chocolat	orage	éclair	gâteau	foudre
capacité	université	faculté	aptitude	école
médecin	céleri	avocat	juriste	tomate
match	fragment	partie	jeu	morceau
gobelet	coiffeur	coupe	verre	cheveux
poker	route	carte	valet	atlas
voiture	capuchon	bouchon	trafic	couvercle
télé	anneau	chaîne	émission	collier
addition	sieste	somme	calcul	repos
aide	cylindre	piston	faveur	moteur

Each polysemous word was associated with two context and two target words respectively associated to both meaning of the polysemous word. Moreover in order to control the absence of semantic relation, each polysemous word was paired with another one (for example *batterie* was paired with *mine*) in order to create all semantic-link conditions (for instance for *batterie*: *Cg* trials= recharge-batterie-pile & tambour-batterie-cymbale; *Icg* trials= recharge-batterie-cymbale & tambour-batterie-pile; *Init* trials= recharge-batterie-stylo & tambour-batterie-charbon; *Sep* trials = recharge-mine-pile & tambour-mine-cymbale; *Ter* trials= crayon-batterie-pile & gisement-batterie-cymbale).

b) Pseudoword-ending trials list in Experiment 1

Context meaning 1	Context meaning2	Polysemous Word	Target meaning 1 /PW	Target meaning 2 /PW
cartable	catégorie	classe	**prourge**	lutte
demande	rangement	ordre	mission	**drompre**
argile	planète	terre	**strourde**	lune
électricité	chasseur	prise	courant	**coutelle**
place	étoile	espace	**sorrame**	univers
anglais	papille	langue	espagnol	**répine**
béquille	pêche	canne	**stromble**	hameçon
bâtiment	cercle	centre	institut	**plime**
sexe	bagnole	capote	**rile**	toit
chef	modèle	patron	directeur	**pressale**
carton	sortie	boite	**recotire**	videur
équation	liquide	solution	problème	**draie**
donjon	voyage	tour	**glattre**	circuit
cheminée	phare	feux	brûlure	**mérieur**
circulation	odorat	sens	**nourse**	vue
optique	sœurs	jumelles	loupe	**ardice**
entrée	lèvre	bouche	**manniche**	dent
main	mer	bras	poignet	**conduile**
ville	portion	quartier	**voise**	tranche
pomme	boxe	pêche	noix	**bouritre**
partition	résultat	note	**concame**	examen
billet	salon	pièce	monnaie	**diconde**
danse	tronche VISAGE	figure	**tratrire**	faciès
haut	collant	bas	milieu	**ritime**
toilette	poire	chasse	**atoire**	safari
arrosoir	avion	jet	eau	**stacte**
photo	pou	pellicule	**sorent**	lotion
bâtard	caisse	baguette	pain	**scastre**
bourse	mouvement	action	**toutrire**	geste
transaction	sac	affaire	finance	**flettre**
amende	tarte	prune	**apance**	abricot
couvée	spécialiste	ponte	oeuf	**rancome**
parquet	gamme	sol	**évertace**	piano
doigt	casque	index	pouce	**plonsace**
bonnet	animal	âne	**dantre**	cheval
buche	cerf	bois	branche	**pouvette**
rythme	distance	mesure	**encide**	règle
chemin	bureau	direction	trajet	**merrive**
situation	pays	état	**scrouve**	nation
nuage	flèche	arc	ciel	**siguve**

For the pseudoword ending trial list, each polysemous word was associated with a pseudoword target (in bold) then, the same method was applied to build trials as for experimental list.

c) Pseudowords in Experiments 2 & 3

Pseudowords in Experiments 2 & 3			
acdique	démete	jaucun	rêpote
acenre	demobe	jusminu	resdine
acerpi	dennatre	juspe	ruide
acipeau	détièle	laistève	rurc
apacle	dodité	lalebe	saber
apose	dougiler	lemi	scame
avain	doulere	maigata	scaud
baque	dressine	mannard	scomb
baxe	druave	marsasé	soudane
beteser	druel	octai	sprorne
biendu	éloce	pacher	spulbe
braoul	finc	pambe	spunte
brifle	flouche	parson	supple
brioleur	fompre	patone	tade
castre	fuquet	percré	tomtobre
cestede	gétine	plygne	toudise
chepule	glongle	poursime	tuivre
clalte	grême	preille	vette
croiler	groc	rece	virail
crouvre	imvanne	repoce	voitre

Discussion générale

Au cours de ce travail, nous avons exploré les processus sémantiques verbaux dans différentes situations:

- Chez des sujets sains conscients et des patients présentant une altération de la conscience (état végétatif et de conscience minimale) : Article 1
- Chez des sujets sains conscients dans des conditions de perception consciente et non consciente: Article 2

Nos résultats peuvent être résumés en cinq points principaux :

1) Nos deux contributions expérimentales apportent des arguments comportementaux et neurophysiologiques robustes en faveur de l'existence de traitements sémantiques verbaux non conscients, à la fois chez le sujet sain et chez certains patients présentant un trouble sévère de la conscience (état végétatif).
2) Sur le plan électrophysiologique nous avons mis en évidence deux signatures cérébrales du traitement sémantique verbal dont l'une est précoce et serait inconsciente (N400) tandis que la seconde est tardive et semble indexer une étape d'accès conscient au contenue sémantique (LPC/P600). Cette dissociation nous a amené à proposer une généralisation d'un modèle à deux étapes de la perception.
3) Dans l'article 2, nous avons mis en évidence pour le traitement sémantique inconscient de nouvelles formes d'influences descendantes conscientes (effets « *top-down* ») en relation avec le contexte expérimental mais aussi avec la stratégie adoptée par les sujets. Ces résultats sont en contradiction avec une conception strictement automatique de la cognition non consciente.
4) Les trois expériences de l'article 2 apportent des éléments nouveaux sur les mécanismes de résolution d'une ambiguïté sémantique mettant en avant les différences entre hémisphères.
5) Enfin concernant l'implication clinique de nos recherches, nous n'avons malheureusement pas été en mesure de mettre au point une procédure suffisamment sensible pour une utilisation à l'échelle individuelle. Néanmoins l'approche utilisée dans le premier article s'est révélée utile pour l'étude à l'échelle d'un groupe de

patients, et permet de discuter de nouveaux développements permettant d'élaborer une méthode sensible et spécifique au niveau individuel.

Notre discussion sera structurée par ces cinq points principaux.

1. Arguments en faveur de l'existence de traitements sémantiques verbaux non conscients

Nous avons abordé la question des relations entre conscience et traitement sémantique verbale en adoptant de manière délibérée une double approche : étude des représentations sémantiques verbales inconscientes chez le sujet non conscient (patient en état végétatif) et chez le sujet conscient (à l'aide d'un paradigme de masquage visuel). Grâce à cette double approche, nous avons découvert des indices comportementaux et neurophysiologiques en faveur de l'existence de telles représentations inconscientes.

Tout d'abord, nous avons pu mettre en évidence un corrélat éléctrophysiologique de traitement sémantique, la N400, chez un groupe de patients en état végétatif (VS). Notre travail vient ainsi s'ajouter à la liste des 6 publications rapportant une N400 chez des patients en état végétatif ou comateux (Schoenle & Witzke, 2004; Kotchoubey, 2005; Kotchoubey, Lang, et al., 2005; Rämä et al., 2010; Steppacher et al., 2012; Balconi et al., 2013). La topographie légèrement différente et la latence plus précoce témoignent probablement de différences qualitatives en termes d'accès sémantique bien que celles-ci soient difficiles à préciser. On peut toutefois noter que l'analyse individuelle n'a permis de détecter une N400 que chez un patient VS contre 5 patients MCS, ce qui suggère l'existence d'une altération plus importante des capacités de traitement sémantique dans le groupe VS. Il est en effet difficile d'imputer cette différence seulement à la différence de niveau de conscience, les patients VS ayant généralement des lésions cérébrales plus importantes que les patients MCS, cette différence est plus probablement liée à des capacités moindres de traitement sémantique indépendantes du niveau de conscience. Une limite réside néanmoins dans notre possible sous-estimation du niveau de conscience des patients considérés comme VS mais, il s'agit là d'une limite inhérente à ce type d'études dans lesquelles, faute de mieux, le « gold standard » reste aujourd'hui la classification clinique.

Ensuite chez le sujet sain, nous avons pu mettre en évidence dans l'article 2 à la fois un effet comportemental et un effet électrophysiologique des mots masqués. Notre paradigme a pris en compte les limites méthodologiques soulevées dans l'introduction (mesure objective de la visibilité des mots masqués, construction rigoureuse du matériel afin d'éviter des effets non sémantiques de type associations pré-établies entre stimulus et réponse). Contrairement à l'hypothèse formulée par Marcel, nous ne trouvons pas d'effet d'amorçage de la représentation non contextualisée des mots polysémiques. Seule la représentation contextualisée conduit à un effet comportemental.

Compte tenu de nos difficultés à obtenir un niveau de masquage visuel permettant d'identifier cet effet d'amorçage, il est important de s'assurer que notre résultat comportemental obtenu dans l'expérience 2 (contraste *Cg* vs *Init*) ne repose pas simplement sur un amorçage conscient entre le premier mot et le mot cible. Comme discuté dans l'article, nous avons pu avancer 3 arguments contre cette hypothèse : 1) Nous n'avons pas observé d'effet d'amorçage du premier mot sur les mots cibles pour les essais masqués de l'expérience 1. Il s'agissait pourtant d'une condition très similaire. 2) Contrairement aux effets d'amorçage conscient, l'effet d'amorçage attribué au mot 2 était sensible au code de réponse. 3) Nous avons également observé cette sensibilité au code de réponse moteur dans l'analyse des PE dans l'expérience 3. Ainsi, l'effet d'amorçage sémantique contextualisé semble effectivement reposer sur un amorçage de la cible par le mot 2 masqué.

Les traitements sémantiques non conscients observés chez les patients et les sujets sains présentent vraisemblablement des différences qui méritent d'être soulignées. En effet alors que dans le premier cas, le sujet n'est pas conscient (au sens intransitif), dans le deuxième cas le sujet est conscient mais inconscient de certaines de ses représentations. Dans cette situation, nos résultats ont mis en évidence plusieurs facteurs d'influence *top down* de la posture consciente du sujet sur ces représentations inconscientes (influences liées au contexte et à la stratégie liée à la tâche). Par définition, de telles modulations sont sans doute absentes dans le premier cas, mais cette hypothèse est évidemment difficile à trancher (tâche à réaliser,…). La comparaison de ces deux formes de traitements inconscients nous renseigne alors peut-être sur des distinctions subtiles entre d'une part des processus inconscients stricts et d'autre part des processus inconscients sous influence consciente. Ainsi l'isolement des effets *top down* sur des processus non conscients pourrait permettre de mieux comprendre l'interaction entre conscience et traitement inconscient, et leur identification chez des patients pourrait constituer une nouvelle classe de marqueurs de traitements conscients : des effets inconscients qui manifestent une sensibilité à des facteurs de modulation consciente.

Nos résultats soutiennent les deux hypothèses formulées en introduction (partie 3.3) :

- H1 : Un traitement sémantique est possible en l'absence de perception consciente.
- H4 : Le premier niveau de traitement sémantique non conscient est observable chez des patients présentant un trouble de la conscience.

2. Modèle du traitement de l'information en deux temps appliqué au traitement sémantique verbal

Nos travaux, bien qu'utilisant un matériel verbal différent, ont révélé de la même manière deux corrélats successifs de traitement sémantique : la N400 suivie de la LPC/P600.

Nous avons vu en introduction les travaux appuyant l'hypothèse que la N400 puisse être un corrélat de traitement sémantique non conscient. L'article de Luck et al. est particulièrement important puisqu'il met en évidence directement une modulation de la N400 de mots non consciemment perçus chez le sujet sain (expérience utilisant la technique du clignement attentionnel ; Luck et al., 1996). De plus la N400 semble observable chez des patients non conscients, celle-ci pourrait donc être considérée comme un corrélat de traitement sémantique non conscient au même titre que la MMN ou la P3a dans un paradigme *odd-ball*.

A l'inverse nous n'avons observé une LPC/P600 que chez des sujets conscients et des patients en état de conscience minimale. Dans l'article 1, l'une des différences majeures entre les deux groupes de patients (VS et MCS) consistait précisément en la présence d'une LPC uniquement dans le groupe MCS. Nous n'avons par ailleurs pas connaissance de travaux rapportant une LPC/P600 en l'absence de traitement conscient. Dans l'article 2 la LPC est pourtant observée dans les deux conditions, masquée et démasquée mais il faut rappeler que les PE décrits sont ceux de la cible, consciemment perçue et non du mot masqué. La LPC observée pourrait être ainsi le reflet d'un processus de ré-analyse (conscient) du mot polysémique et/ou du premier mot à la faveur du nouveau contexte définit par la cible (voir ci dessous partie 3). Comme mentionné dans l'introduction de ce travail (partie 1.3.2), la LPC/P600 a été initialement décrite comme un marqueur de violation syntaxique (Friederici, 2004) puis elle a ensuite été rapportée dans plusieurs types de paradigmes, et notamment dans des manipulations strictement sémantiques sans manipulation syntaxique (Hill et al., 2002; Grieder et al., 2012) Ce PE a également été observé dans des expériences sondant de hauts niveaux d'abstraction tels que l'ironie ou la métaphore (Regel, Gunter, & Friederici, 2011;

Spotorno, Cheylus, Van Der Henst, & Noveck, 2013; De Grauwe, Swain, Holcomb, Ditman, & Kuperberg, 2010) . Enfin la LPC/P600 partage une latence (200 ms après la première étape) et une topographie similaire à la P3b. Etant donné que la P3b a été proposée comme un marqueur d’accès conscient (Vogel, Luck, & Shapiro, 1998; Sergent et al., 2005), ces similarités font de la LPC/P600 un excellent candidat de marqueur de traitement sémantique conscient.

Plusieurs travaux soutiennent déjà l’idée d’un traitement sémantique en deux temps: premier temps non conscient (dont le corrélat serait la N400) éventuellement suivi d’un deuxième temps conscient (dont le corrélat serait la LPC/P600) (Marinkovic et al., 2003; Gaillard et al., 2009). Alors que le premier niveau de traitement serait confiné à un réseau « local » , le deuxième niveau correspondrait à la mise en jeu « global » de plusieurs régions notamment associatives (en particulier le cortex préfrontal et pariétal ; voir introduction partie 2) via une augmentation de la connectivité à longue distance (Gaillard et al., 2009). Ce modèle à deux temps est par ailleurs en accord avec plusieurs modèles de la conscience et en particulier avec celui du l’espace de travail global (ou GNW pour *Global Neuronal Workspace*; Dehaene & Naccache, 2001; Lamme, 2006; Dehaene et al., 2006; Sergent & Naccache, 2012).

Nos résultats vont donc dans le sens de deux hypothèses formulées en introduction (partie 3.3) :

- H2 : Le modèle de traitement de l’information à deux temps, dérivé de la théorie de l’espace de travail global neuronal conscient, peut s’appliquer au traitement sémantique: Un premier niveau de traitement non conscient serait suivi d’un second niveau de traitement conscient sensible au contexte.
- H5 : Le deuxième niveau de traitement sémantique conscient, est observable uniquement chez des patients présentant un espace de travail global fonctionnel donc conscient ou au moins MCS.

3. Influences *top-down* sur les traitements sémantiques conscients et non conscients

Les trois expériences de l’article 2 nous ont permis de mettre en évidence plusieurs types d’influences de la posture consciente portant à la fois sur les mot polysémiques consciemment perçus mais aussi sur les mots polysémiques masqués. Ces résultats sont en contradiction avec une conception strictement automatique de la cognition non consciente.

Observation d’un effet d’amorçage polysémique conscient

Dans la première expérience, nous avons mis en évidence un effet d’« amorçage polysémique conscient», c’est à dire une activation des deux représentations du mot polysémique en condition consciente. Un tel effet d’amorçage polysémique conscient a déjà été rapporté, pour des SOA courts (SOA <300 ms; Swinney, 1979; Onifer & Swinney, 1981) constituant d’ailleurs un des principaux arguments soutenant le « modèle de l’accès multiple » dans lequel il y aurait un accès initial aux différentes représentations d’un mot polysémique suivi d’une inhibition des représentations non congruentes. Cependant à la différence des travaux cités, notre « amorçage polysémique conscient » a la particularité de survenir pour un SOA long (500 ms). De plus il n’a été observé que chez la moitié des sujets : ceux ayant réalisé le bloc démasqué dans la deuxième moitié de l’expérience. Ces sujets ont plus souvent pris conscience du caractère polysémique des mots comparativement à ceux qui ont passé la partie démasquée en premier et qui ne présentent pas d’amorçage polysémique. Cette différence peut certes être en partie liée à un effet mémoire mais pourrait aussi s’expliquer soit par une absence d’amorçage multiple soit par une inhibition précoce des représentations alternatives qui surviendrait avant la prise de conscience chez les sujets ayant réalisé le bloc démasqué en premier. On peut remarquer que la rapportabilité du caractère polysémique du matériel utilisé est malheureusement rarement renseignée dans les divers travaux cités alors que c’est un élément majeur pour l’interprétation des résultats en condition consciente (Swinney, 1979; Onifer & Swinney, 1981).

Une des hypothèses permettant d’expliquer ces résultats pourrait consister à faire intervenir un relâchement du contrôle exécutif préfrontal lié à la fatigue. L’allongement notable des temps de réponse dans la deuxième partie de l’expérience va dans ce sens. De plus dans l’expérience 2 nous avons volontairement et avec succès fait disparaître cet effet en raccourcissant la durée de l’expérience, ce qui conforte notre hypothèse.

Plusieurs travaux mettent en avant le rôle du cortex préfrontal dans la sélection d'une représentation sémantique (gyrus frontal inférieur gauche –LIFG notamment ; Thompson-Schill, Esposito, Aguirre, & Farah, 1997; Rodd, Vitello, Woollams, & Adank, 2015) et en particulier pour les mots polysémiques (Rodd, Davis, & Johnsrude, 2005; Ihara, Hayakawa, Wei, Munetsuna, & Fujimaki, 2007; Zempleni, Renken, Hoeks, Hoogduin, & Stowe, 2007). Les patients présentant un trouble du langage en rapport avec une lésion préfrontale gauche (LIFG, aphasie de Broca) ont des difficultés à extraire la bonne représentation d'un mot polysémique contextualisé (Hagoort, 1993; Swaab, Brown, & Hagoort, 2003; Hagoort, 2005) alors que la stimulation de cette région chez des sujets sains au moyen de la tDCS améliorerait les performances de résolution d'ambiguïté (Ihara et al., 2014). D'autres auteurs soulignent l'implication bilatérale du cortex préfrontal (pars opercularis notamment ; Bilenko, Grindrod, Myers, & Blumstein, 2009; Klepousniotou, Gracco, & Pike, 2014) ou l'implication d'un réseau plus vaste (cortex préfrontal dorso-latéral (DLPFC) gauche, partie ventro-médiale du lobe temporal gauche, et de manière bilatérale encore, gyrus angulaire (AG) et partie antérieure du gyrus temporal supérieur (aSTG ; Hoenig & Scheef, 2009; Zempleni et al., 2007). Ces résultats vont dans le sens de notre hypothèse qu'un relâchement du contrôle exécutif pourrait permettre un amorçage multiple en condition consciente.

Selon cette hypothèse, il est intéressant de noter que l'existence d'une sélection contextuelle d'une représentation d'un mot polysémique consciemment perçu ne surviendrait pas de manière automatique : la perception consciente du mot constituerait une condition nécessaire mais non suffisante de cet effet. Autrement dit, ce processus de sélection qui nécessiterait un accès conscient ne constituerait pas un attribut inhérent au traitement conscient du stimulus.

Enfin, nous ne pouvons exclure que la présence d'un amorçage des deux représentations sémantiques du mot polysémique dans le groupe des sujets « fatigués » soit due à l'absence d'effet de contextualisation du premier mot. Une telle hypothèse permettrait en effet de donner sens à nos résultats de manière parcimonieuse : les deux sens du mots seraient activés du fait de l'absence de filtre initial lié au contexte.

Absence d’amorçage polysémique inconscient ?

Dans les expériences 2 et 3, nous montrons respectivement un effet comportemental puis électrophysiologique de la représentation contextualisée du mot polysémique sous la forme d’une positivité postérieure gauche dans la fenêtre de la N400. Nous retrouvons également une topographie similaire, bien que fortement atténuée, pour la représentation non contextualisée dans la même fenêtre temporelle. Ces résultats montrent que le traitement sémantique inconscient d’un mot polysémique est très dépendant du contexte, au même titre que le traitement conscient. Ils vont donc contre l’hypothèse de Marcel qui suggérait une activation des différentes représentations d’un mot polysémique en l’absence de perception consciente. Récemment, en explorant l’amorçage polysémique non conscient à l’aide de SOA variables (100 à 1500 ms), une autre équipe a retrouvé des résultats similaires aux nôtres (Eckstein, Kubat, & Perrig, 2011). En comparant les effets de la représentation la plus fréquente d’un mot polysémique (représentation « dominante ») avec une représentation « subordonnée », ces auteurs montrent un amorçage restreint à la représentation dominante en condition masquée.

L’observation des PE obtenus dans la fenêtre tardive de la LPC/P600 pourrait en revanche suggérer qu’un accès multiple soit possible en l’absence de conscience puisqu’on observe un effet prenant la forme d’une négativité frontale identique pour les deux représentations, congruente et incongruente. Cet effet impliquerait la persistance (ou l’activation tardive) des différentes représentations du mot polysémique qui ne seraient alors accessibles que lors de la fenêtre tardive du traitement de la cible (soit environ 700 ms après la présentation du mot polysémique). L’absence d’effet comportemental dans ce cas s’explique par le caractère tardif de cette « ré-activation », survenant légèrement après la réponse du sujet (560 ms en moyenne dans l’expérience 2). Cependant un tel traitement tardif n’est pas nécessairement le témoin d’un accès sémantique car une trace lexicale du mot masqué pourrait tout aussi bien conduire à de tels effets. Plus généralement ce résultat doit être considéré de concert avec les autres particularités de cette réponse tardive. Nous avons en effet observé une modulation de cette composante tardive du mot cible à chaque fois que celui-ci était précédé par un ou deux mots partageant un lien sémantique avec lui (*Cg, Icg et Sep*). Ainsi, cet effet pourrait refléter un processus remontant à l’envers l’ordre des stimuli délivrés : le mot cible consciemment perçu pourrait dans la phase tardive de son traitement devenir lui-même de manière rétroactive un indice contextuel. Toutes les traces des mots présentés précédemment lors de l’essai (mots 1 et 2) pourraient alors être rétroactivement amorcées par le mot cible. Cette hypothèse est supportée par les travaux récents de Claire Sergent qui révèlent l'existence d'effets rétroactifs de l'attention spatiale sur des représentations non conscientes (Sergent et al., 2013). Si elle était vérifiée, notre hypothèse signifierait qu'une représentation inconsciente infra-sémantique (par exemple lexicale) du mot 2 serait encore amplifiable après la présentation du mot cible. L'absence d'influence du code de réponse sur cet effet serait prédite par cette hypothèse. Des expériences futures seront nécessaires afin de vérifier le bien-fondé de cette hypothèse abductive.

Sérendipité : Effet lié au code de réponse

En plus de l'effet lié au contexte, nous avons découvert un effet lié au code de réponse uniquement sur l'amorçage masqué. Cet effet qui ne faisait pas partie de nos hypothèses soulève un certain nombre de questions.

En effet si l'utilisation de code de réponses manuelles spécifiques avait été envisagée par certains pour explorer les différences de performance lexicale entre hémisphère droit (HD) et hémisphère gauche (HG), cette stratégie s'est avérée bien moins efficace que la présentation par hémi-champs visuels. Dans une série d'expériences visant spécifiquement à quantifier l'influence du code de réponse, Weems & Zaidel ont pu montrer l'absence d'effet significatif, que ce soit pour le code que nous avons utilisé, ou pour d'autres codes (Weems & Zaidel, 2005). La main gauche pourrait donc profiter très facilement des performances de l'HG, tout du moins en condition consciente.

A la différence du code de réponse, la présentation de stimuli par hémi-champ visuel a permis d'obtenir de nombreux résultats intéressants. Ainsi l'hémisphère droit a été impliqué dans certains processus complexes de compréhension du langage. L'hémisphère droit permettrait notamment l'accès à un répertoire de représentations sémantiques plus vaste que le gauche facilitant ainsi la mise en relation de concepts distants. Il semblerait par ailleurs qu'il soit moins sensible au phénomène d'amorçage sémantique (Taylor, Brugger, Weniger, & Regard, 1999; Chiarello, Liu, Shears, Quan, & Kacinik, 2003). L'hémisphère gauche serait quant à lui plus rapide mais beaucoup plus sélectif et donc d'avantage sensible à l'amorçage sémantique (Jung-Beeman, 2005). Concernant la polysémie, une dissociation intéressante apparaît entre HG et HD : dans l'HG la représentation « dominante » (représentation la plus fréquente d'un mot polysémique présentant une asymétrie en termes de fréquence de ses représentations) serait activée précocement (<100 ms) puis maintenue (jusqu'à au moins 750 ms) alors que la représentation « subordonnée » serait rapidement inhibée. Inversement, dans l'HD, l'activation de la représentation « dominante » serait suivie d'une activation tardive de la représentation « subordonnée » (Burgess & Simpson, 1988; Titone, 1998; Atchley, Keeney, & Burgess, 1999; Atchley, Burgess, & Keeney, 1999; Faust & Lavidor, 2003). Ces résultats ont pu être répliqués en modalité auditive (Atchley, Grimshaw, Schuster, & Gibson, 2011).

A la lumière de ces travaux les résultats de l'expérience 2 pourraient s'interpréter de deux manières différentes : 1) En condition consciente l'HG plus rapide et plus sensible à l'amorçage dominerait l'HD et l'effet d'amorçage ne s'observerait que pour la représentation contextualisée du mot polysémique quelque soit le code de réponse utilisé. En condition masquée, le traitement sémantique du mot masqué ne dépendrait pas du code de réponse et aurait lieu dans un réseau hémisphérique gauche localisé. Cette information resterait confinée à l'HG du fait de l'absence d'amplification consciente dans l'espace de travail global (Dehaene & Naccache, 2001; Schmidt, Palminteri, Lafargue, & Pessiglione, 2010). Ainsi l'effet d'amorçage ne serait visible dans l'analyse des temps de réponse que pour la condition «main droite pour mot » du fait du caractère localisé à l'HG du traitement sémantique inconscient. 2) Le traitement sémantique non conscient réalisé par l'HG serait dépendant du code de réponse, c'est à dire de la stratégie adoptée par le sujet et donc plus généralement de sa posture consciente. Les résultats de l'expérience 3 vont dans le sens de cette deuxième hypothèse puisque nous n'avons pas observé d'effet d'amorçage lorsque les sujets utilisaient le code « main gauche pour mot » dans la fenêtre de la N400.

Le traitement sémantique inconscient de mots polysémiques serait donc au même titre que le traitement conscient sensible aux influences *top-down* définies par le contexte. Par ailleurs contrairement au traitement conscient, le traitement sémantique inconscient réalisé par l'HG. serait dépendant de la tâche.

Nos résultats vont donc dans le sens de l'hypothèse H3 formulée en introduction (partie 3.3) : Le premier niveau de traitement sémantique non conscient peut être sensible aux influences *top-down* conscientes, et n'est donc pas automatique au sens fort du terme.

4. Intégration de nos résultats aux modèles de résolution d’ambiguïté sémantique

Alors que l’ambiguïté sémantique est extrêmement répandue (80 % des mots communs en anglais sont ambigus ; Rodd, Gaskell, & Marslen-Wilson, 2002), la question des mécanismes psychologiques et cérébraux permettant sa résolution n’est à ce jour pas encore tranchée. Dès la publication des premiers travaux cherchant à comprendre ces mécanismes, trois principaux modèles ont été proposés : 1) le « modèle de l’accès multiple » dans lequel il y aurait un accès initial aux différentes représentations suivi d’une inhibition des représentations non congruentes au contexte ; 2) le « modèle dépendant du contexte » dans lequel seule la représentation congruente au contexte serait activée et 3) le « modèle de l’accès unique » dans lequel les différents sens seraient accédés en série, en commençant par le plus fréquent, jusqu’à ce que celui congruent au contexte émerge (Simpson, 1984; Burgess & Simpson, 1988). Ainsi que nous l’avons énoncé dans les parties précédentes, de nombreuses études comportementales (amorçage polysémique pour des SOA courts) et d’imagerie fonctionnelle (mise en jeu de régions préfrontales dans la résolution d’une ambiguïté sémantique) plaident en faveur du modèle de l’accès multiple et c’est sur la base de ce modèle que nous avons choisi d’utiliser la polysémie afin d’explorer les différences entre les traitements sémantiques conscients et non conscients.

Nos résultats ne sont finalement que partiellement en accord avec le modèle de l’accès multiple. En effet nous retrouvons une très forte influence du contexte s’exerçant probablement au travers de processus attentionnels dépendant des fonctions exécutives préfrontales (expérience 1). Cet effet du contexte semble extrêmement précoce comme en témoigne l’absence d’amorçage de la représentation non contextualisée à court SOA (100 ms). Cela suggère soit que la représentation non contextualisée n’ait pas encore été activée, soit qu’elle ait déjà été inhibée. L’observation en PE d’une topographie similaire à celle de la représentation contextualisée, bien que d’amplitude moindre est compatible avec ces deux interprétations. Dans la publication récente de Eckstein, l’absence d’amorçage polysémique en condition masquée est interprétée comme une inhibition qui surviendrait dès 100 ms en raison de temps de réponse allongés pour la représentation « subordonnée » (Eckstein et al., 2011). Dans nos trois expériences, nous ne retrouvons pas cet effet d’allongement des RT pour la représentation non contextualisée, ces résultats sont donc plutôt en faveur d’une absence d’activation de la représentation non contextualisée en raison de l’effet du contexte, c’est-à-dire d’un modèle dépendant du contexte.

Cependant l’effet observé dans la fenêtre tardive de la LPC/P600 pourrait bien témoigner de la persistance d’une activation de la représentation non contextualisée au moment du traitement tardif de la cible. Cet effet tardif pourrait correspondre à une composante de la LPC/P600 et être alors en rapport avec une tentative d’intégration du mot masqué au nouveau contexte défini par la cible. Comme détaillé plus haut, la LPC/P600 a en effet été rattachée à des processus de ré-analyse sémantique et syntaxique complexes comme l’ironie ou la métaphore. Cependant comme nous l’avons déjà dit, ce traitement tardif ne préjuge pas forcement d’un accès sémantique et une trace lexicale du mot polysémique masqué pourrait tout aussi bien conduire à de tels effets.

Enfin l’effet du code de réponse en condition de masquage et les travaux cités évoquant l’asymétrie hémisphérique en termes de sensibilité à l’amorçage sémantique (partie 3) suggèrent un rôle prépondérant de l’HG dans le phénomène d’amorçage sémantique de la représentation contextualisée. Par ailleurs contrairement au traitement conscient, les performances de l’hémisphère gauche en condition non consciente seraient sensibles à la tâche réalisée par le sujet. A l’inverse, l’activation de la représentation non contextualisée suggérée par l’effet observé dans la fenêtre de la LPC est insensible au code de réponse ce qui permet de suggérer un rôle de l’HD (ou des deux hémisphères). Ces résultats, mis en perspective avec les résultats des études s’intéressant aux différences en termes de traitement sémantique entre hémisphères, permettent d’imaginer une dissociation entre hémisphères. Dans un tel scénario, l’HG fonctionnerait selon un modèle dépendant du contexte alors que l’ HD fonctionnerait quant à lui selon un modèle d’accès multiple.

Nos résultats sont donc sensiblement différents de ceux rapportés dans la publication princeps de Marcel qui ont inspirés nos travaux. Les nouvelles connaissances relatives à la cognition inconsciente permettent néanmoins de suggérer une interprétation alternative de ses résultats. En effet plusieurs travaux ont montré le caractère évanescent des représentations inconscientes (Greenwald et al., 1996; Naccache, Blandin, & Dehaene, 2002). Le long SOA utilisé par Marcel (600 à 1500 ms) entre le mot masqué et la cible suggère donc fortement que l’effet d’amorçage qu’il a observé soit en rapport avec une représentation consciente des mots polysémiques. Nous avons vu par ailleurs la remise en question de l’invisibilité des mots masqués des expériences réalisées à cette époque. Enfin les résultats de l’expérience 1 ont montré l’importance de la prise en compte du contexte dans la réduction de la polysémie. On peut donc imaginer un scénario dans lequel des mots polysémiques insuffisamment masqués aient pu être traités consciemment par les sujets moyennant un effort attentionnel important et au dépend du premier mot. Cette diminution de la contextualisation des mots polysémiques consciemment traités pourrait expliquer les résultats obtenus par Marcel.

5. Implications cliniques

L’étude des capacités de traitement sémantique de patients cérébro-lésés constitue un enjeu important dans une perspective d’amélioration de nos outils diagnostiques et à visée pronostique.

Dans le premier article, nous avons fait le choix d’utiliser un paradigme d’amorçage sémantique classique, et d’enregistrer les PE afin de détecter les signatures cérébrales du traitement des attributs sémantiques des mots délivrés. Cette technique présente l’avantage de pouvoir être réalisée au lit du patient et de permettre une analyse à la résolution temporelle optimale (échelle de la milliseconde). Malheureusement dans notre étude, le manque de sensibilité de ce paradigme la rend peu utile en pratique clinique. Il est intéressant de noter que parmi les 6 publications citées ayant utilisé une approche similaire, seules 5 rapportaient des données individuelles (Schoenle & Witzke, 2004; Kotchoubey, Daltrozzo, et al., 2005; Kotchoubey, Lang, et al., 2005; Rämä et al., 2010; Steppacher et al., 2012) et qu’aucune ne comportait de groupe contrôle permettant d’évaluer la sensibilité de la méthode. Par ailleurs, l’évaluation de la présence de corrélat de traitement sémantique ne s’appuyait sur aucune statistique prenant en compte la variance à travers les essais et ne reposait donc que sur l’analyse visuelle des courbes moyennées. Récemment Cruse et al. ont justement cherché à évaluer les performances d’une méthode de PE similaire en utilisant une approche statistique rigoureuse semblable à celle que nous avons utilisée dans l’article 2 (*cluster based permutation* dans le logiciel Fieldtrip). Ils sont arrivés aux mêmes conclusions que nous : la technique classique de recherche de la N400 n’est pas assez sensible pour être utilisée en clinique (Cruse et al., 2014). Ces auteurs et d’autres soulignent par ailleurs l’influence de la tâche réalisée par les sujets dans l’amplitude des réponses observées : en écoute passive la N400 est systématiquement moins ample - bien que présente - comparativement à celle obtenue dans une tâche active (Perrin & García-Larrea, 2003; Relander, Rämä, & Kujala, 2009).

La technique du « *Triple Threshold* » que nous avons utilisée dans l'article 1 est moins conservatrice que les tests non paramétriques statistiquement plus rigoureux. Elle est donc plus sensible mais conduit nécessairement à un taux de faux positifs plus important. D'autres types d'analyses statistiques pourraient être intéressants, comme par exemple l'utilisation de décodeurs multivariés permettant de décoder le signal à l'échelle d'un essai (King, Faugeras, et al., 2013), de même que l'analyse en temps-fréquence qui a montré son utilité dans le travail de Steppacher (2012). Par ailleurs, une des solutions envisagées pour espérer obtenir une meilleure sensibilité consisterait à utiliser des conditions plus contrastées comme par exemple « mots » et « pseudo-mots ». Une étude actuellement en cours dans notre équipe donne pour l'instants des résultats prometteurs chez des sujets contrôles. L'utilisation de mots porteurs ou non d'une valence émotionnelle pourrait permettre là encore d'augmenter la sensibilité de détection de corrélats électrophysiologiques de traitements sémantiques verbaux.

L'évaluation diagnostique et pronostique des patients cérébro-lésés présentant un trouble de la conscience s'est profondément modifiée ces dernières années. L'exemple le plus parlant est sans doute celui du coma post-anoxique pour lequel l'utilisation de plus en plus large de l'hypothermie thérapeutique a modifié sensiblement les performances de marqueurs pronostiques tels que certains signes cliniques, l'EEG ou les PE somesthésiques (Greer, Rosenthal, & Wu, 2014; Taccone et al., 2014). De ce fait que ce soit au moment de la prise en charge en réanimation ou de manière plus tardive, l'exploration des patients non communicants tend actuellement vers une approche multimodale associant par exemple à la clinique et aux explorations fonctionnelles des techniques d'imagerie quantitative telles que le tenseur de diffusion ou la spectroscopie par résonnance magnétique (Galanaud & Puybasset, 2010; Galanaud et al., 2012; Luyt et al., 2012; Stevens, Hannawi, & Puybasset, 2014). Ce changement de paradigme au profit d'une imagerie quantitative permet de dépasser la simple analyse visuelle et d'établir des corrélations entre lésion et pronostic sur de larges cohortes.

L'équipe de Jacques Luauté et Catherine Fischer a pu montrer l'impact pronostique de la distinction entre patients VS et MCS (Luauté et al., 2010) et il est fort probable que tous ces nouveaux outils venant compléter l'expertise clinique et l'imagerie morphologique permettront de dépasser la clinique parfois peu nuancée entre ces quatre états que sont le coma, l'état végétatif, l'état de conscience minimale et l'état conscient. Cette réflexion vise surtout les deux catégories cliniques intermédiaires dont les distinctions ne sont pas évidentes, et qui semblent surtout très hétérogènes du point de vue cognitif. De plus, de tels marqueurs indirects pourront être utiles pour évaluer de nouvelles approches thérapeutiques. Par exemple, Castro et al. ont pu montrer un effet bénéfique de la musique sur la réponse électrophysiologique au propre prénom, corrélée à une meilleurs évolution clinique (Castro et al., 2015). D’autres approches thérapeutiques déjà en cours, telles que la stimulation cérébrale profonde, la tDCS ou les approches pharmacologiques pourront bénéficier de ces avancées. Enfin cette meilleure stratification sera fondamentale afin de proposer les thérapeutiques adaptées à chaque patient.

Conclusions et perspectives

L’étude de fonctions cognitives aussi complexes que le langage, la conscience et a fortiori leurs relations, constitue un vrai défi scientifique. Le traitement sémantique procure à nos expériences perceptuelles un niveau de représentation abstrait, permettant une variété de fonctions conceptuelles telles que la reconnaissance d’objet, la cognition sociale, le langage mais aussi cette capacité remarquable de nous remémorer le passé et d’imaginer le futur. Nous avons pu identifier certaines relations entre traitement sémantique et conscience, mais l’« histoire » ne fait que commencer. L’évaluation des capacités de traitement sémantique chez les patients présentant un trouble de la conscience pourrait permettre d’améliorer sensiblement nos capacités pronostiques. Le pronostic de retour à la conscience serait ainsi enrichi par un paramètre qualitatif concernant le contenu et les possibilités d’interaction de cette conscience.

Cette recherche se situe aux confins de la médecine (réanimation, anesthésie, neurologie) et des neurosciences cognitives fondamentales et nous propose une palette de nouveaux outils prometteurs. Ces développements appellent cependant une expertise clinique neurologique rigoureuse des états de conscience. Une évaluation clinique de grande qualité est en effet indispensable pour intégrer ces données complémentaires en cours de développement au raisonnement médical afin de préciser l’état actuel ainsi que le pronostic d’un malade. Ces nouveaux développements ouvrent également des questions éthiques en rendant théoriquement possibles des situations inédites telles que le recueil d’une réponse volontaire chez un malade non communicant.

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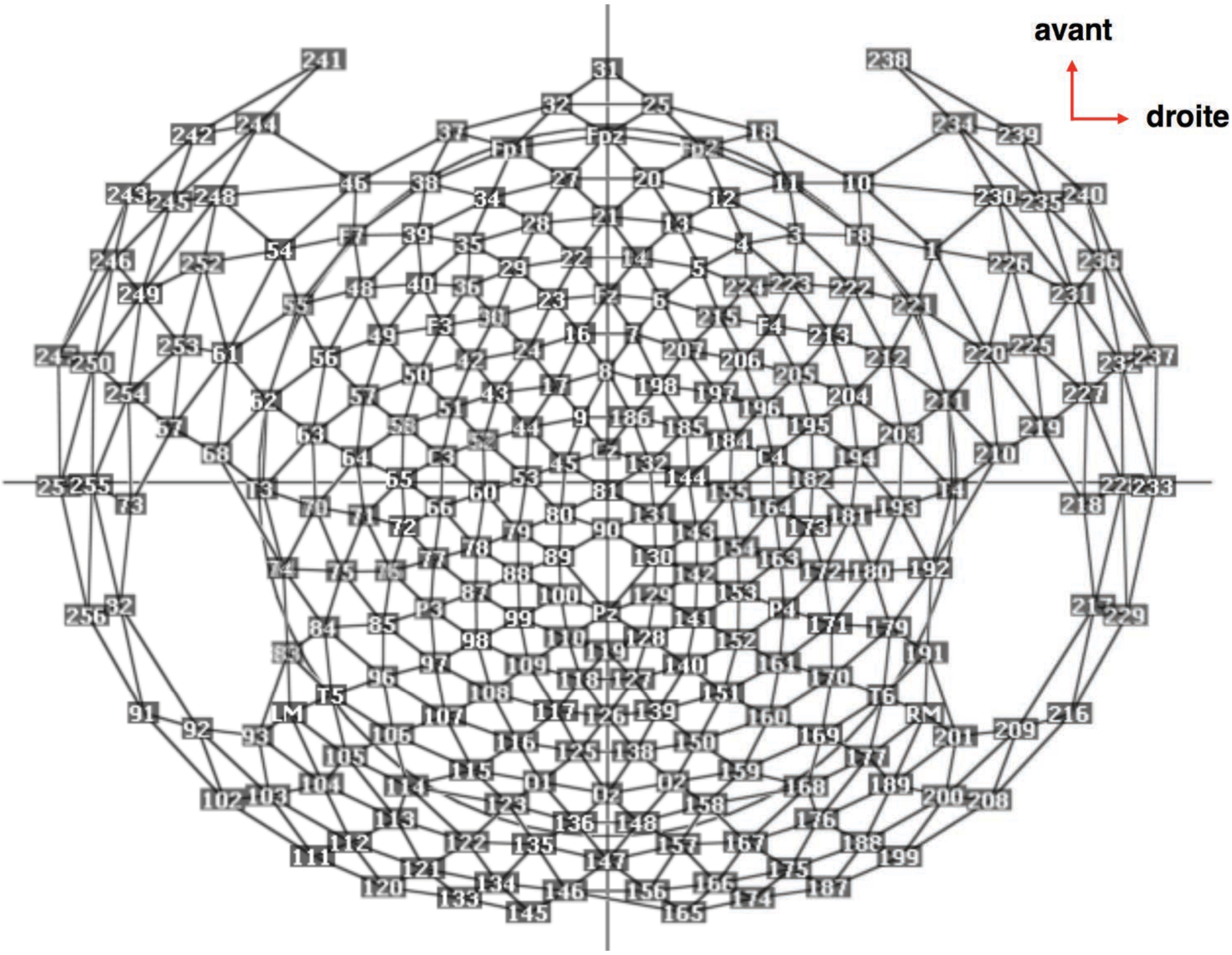
Annexes



Annexe 1 Emplacement des 256 électrodes d’un casque EEG EGI

Annexe 2

Neural signature of the conscious processing of auditory regularities

Tristan A. Bekinschtein[a], Stanislas Dehaene[a,b], Benjamin Rohaut[a], François Tadel[a], Laurent Cohen[a,c,d], and Lionel Naccache[a,c,d,1]

[a]Cognitive Neuro-Imaging Unit, Institut Fédératif de Recherche 49, Institut National de la Santé et de la Recherche Médicale, 91191 Gif sur Yvette, France; [b]Neurospin Center, Commissariat à l'Energie Atomique, I2BM, 91191 Gif sur Yvette, France; [c]Pôle des Maladies du Système Nerveux, Assistance Publique Hôpitaux de Paris, Hôpital de la Pitié-Salpêtrière, 75013 Paris, France; and [d]Pôle des Maladies du Système Nerveux, Université Pierre et Marie Curie Paris 6, 75005 Paris, France

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Can conscious processing be inferred from neurophysiological measurements? Some models stipulate that the active maintenance of perceptual representations across time requires consciousness. Capitalizing on this assumption, we designed an auditory paradigm that evaluates cerebral responses to violations of temporal regularities that are either local in time or global across several seconds. Local violations led to an early response in auditory cortex, independent of attention or the presence of a concurrent visual task, whereas global violations led to a late and spatially distributed response that was only present when subjects were attentive and aware of the violations. We could detect the global effect in individual subjects using functional MRI and both scalp and intracerebral event-related potentials. Recordings from 8 noncommunicating patients with disorders of consciousness confirmed that only conscious individuals presented a global effect. Taken together these observations suggest that the presence of the global effect is a signature of conscious processing, although it can be absent in conscious subjects who are not aware of the global auditory regularities. This simple electrophysiological marker could thus serve as a useful clinical tool.

consciousness | neuroimaging | neurophysiology | patients

When we perceive a stimulus, our brain generates a complex pattern of neural activity, reflecting the summation of a large number of information-processing stages, some of which correspond to the conscious processing of perceived representations, whereas others reflect nonconscious processing. How could we disentangle the respective correlates of conscious and nonconscious perception within the same experimental paradigm using neurophysiological measures? From a clinical perspective, designing a simple neurophysiological test that could selectively monitor conscious-level processing and assess its integrity would be extremely useful for patients suffering from coma, persistent vegetative or minimally conscious states.

Neurophysiological monitoring of the perceptual categorization of a rare auditory deviant stimulus delivered within a serial flow of frequent standard stimuli offers a relevant step toward this goal. A rich literature demonstrates that the detection of novel auditory stimulus includes 2 distinct neural events, a mismatch negativity response (MMN) (1) followed by a later neural response labeled P300 (P3a and P3b) complex (2, 3). The respective properties of these 2 responses suggest that the MMN mostly reflects a preattentive, nonconscious response (4), whereas the late component of the P300 complex (P3b) has been theorized as an index of working memory updating (5) and is empirically associated with conscious access (6). The P3b component has been shown to be insensitive to interstimulus intervals (ISI) exceeding tens of seconds, and has even been observed for ISI as long as 10 min (7), thus implying an active maintenance of previous stimuli in conscious working memory. In sharp contrast, the MMN vanishes when the ISI exceeds a few seconds (8), suggesting a fast decay characteristic of nonconscious iconic memory (9, 10). In addition to this temporal distinction between MMN and P3b responses, MMN (and P3a) are largely resistant to top-down and attentional effects. They can even be observed during rapid eye-movement sleep (11) and anesthesia (12), and in unconscious comatose (13–15) or vegetative state patients (16, 17) or in response to visual subliminal stimuli (18, 19), whereas the P3b is highly dependent on attention and conscious awareness of the stimulus (6, 20).

Still, MMN and P3b events are close in time, sometimes difficult to differentiate, and the fine distinction between P3a and P3b makes it extremely difficult to identify with certainty a P3b component in individual subjects. To circumvent these limitations, we designed a paradigm in which 2 embedded levels of auditory regularity are defined, respectively at a local (within trial) and at a global (across trials) time scale. We predicted that violations of the local regularity should elicit measurable ERPs in both conscious and nonconscious conditions, but that violations of the global regularity should be detected only during conscious processing. In other words, the presence of an ERP signature of violation of the global regularity in an individual subject would be diagnostic of conscious processing. The auditory channel was chosen because we aimed at using this test with non communicating human patients, in whom auditory stimulation is easy to deliver and elicits robust activations without requiring active eye opening.

To validate our paradigm, we first analyzed its brain mechanisms with high temporal and spatial resolutions by combining high-density scalp ERP, intracerebral LFP, and fMRI measurements in conscious subjects submitted to distinct experimental manipulations of their consciousness of the stimuli. We then probed the scientific and clinical potential of our test by recording 8 noncommunicating patients either in the vegetative state (VS) or in the minimally conscious state (MCS). VS is a clinical condition lacking any behavioral sign of conscious processing despite a preserved waking state. MCS is a condition characterized by intermittent and discrete signs of conscious processing (*21*).

Results

The ERP Local-Global Paradigm. On each trial, a series of 5 brief sounds was presented over a total of 650 ms (see Fig. 1*A*). The first 4 sounds were always identical, either high or low-pitched, whereas the fifth sound could be identical (locally standard trials) or different (locally deviant trials) to the preceding ones. In distinct experimental blocks, global regularity was defined according to the relative frequency of the 2 types of elementary trials. Globally

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Author contributions: T.A.B., S.D., and L.N. designed research; T.A.B., B.R., and L.N. performed research; T.A.B., B.R., F.T., and L.N. analyzed data; and T.A.B., S.D., L.C., and L.N. wrote the paper.

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[1] To whom correspondence should be addressed. E-mail: lionel.naccache@psl.aphp.fr.

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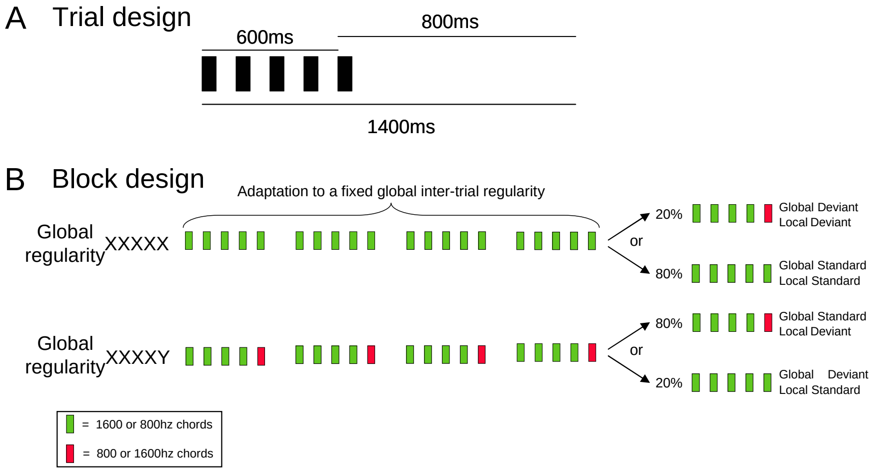

Fig. 1. Experimental design. (*A*) On each trial 5 complex sounds of 50-ms-duration each were presented with a fixed stimulus onset asynchrony of 150 ms between sounds. Four different types of series of sounds were used, the first 2 were prepared using the same 5 sounds (AAAAA or BBBBB), and the second 2 series of sounds were either AAAAB or BBBBA. (*B*) Each block started with 20–30 frequent series of sounds to establish the global regularity before delivering the first infrequent global deviant stimulus.

standard trials were delivered pseudorandomly on 80% of trials, whereas the global deviant trials were presented with a frequency of 20%. Importantly, local and global regularities could be manipulated orthogonally, thus defining 4 types of trials: local standard or deviant, and global standard or deviant (see Fig. 1*B*). All subjects were presented with these 4 conditions. Each block started with 20–30 global standard trials to establish the global regularity before the occurrence of the first global deviant trial.

In Experiment 1, 11 normal volunteers were instructed to actively count the number of global deviant trials while high-density recordings of scalp ERPs were collected. The local and global effects affected distinct time windows of the averaged ERPs. Violation of the local regularity (local deviant: local standard ERPs) was associated with 2 successive electrical events: first a vertex centered mismatch negativity appeared ≈130 ms after the onset of the fifth sound, followed by a central positivity with simultaneously bilateral occipito-temporal negativities ranging from 200 to 300 ms (see Fig. 2). Violation of the global regularity correlated with a central positivity, simultaneous to a frontal negativity, which appeared ≈260 ms after the onset of the fifth sound, and persisted until the end of the 700 ms epoch of interest. Interestingly, a late temporal window (320–700 ms) was affected only by the violation of the

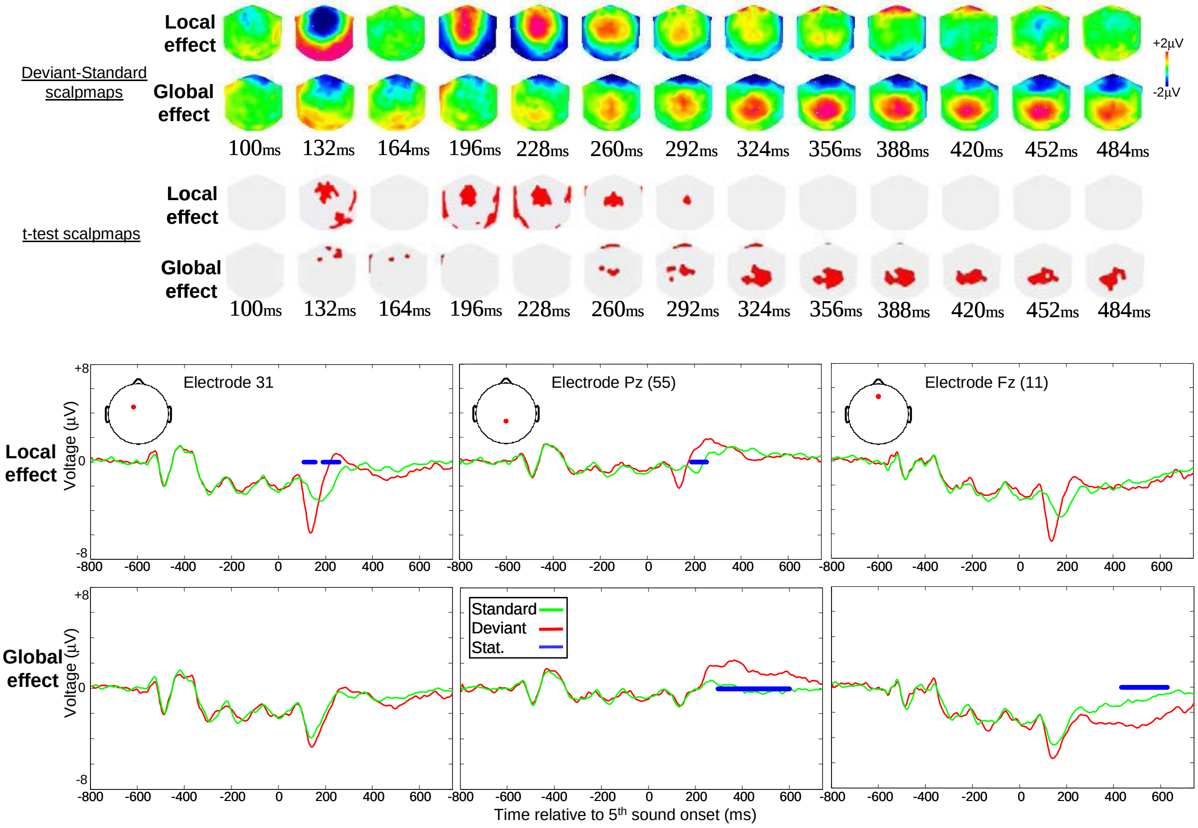

Fig. 2. Local and global ERP effects in the active counting task. Averaged voltage scalpmaps of the local and global subtractions (deviant minus standard) are plotted (top) from 100 to 484 ms after the onset of the fifth sound. Corresponding thresholded t tests scalpmaps (red) are shown for each condition. ERPs of 3 representative electrodes are shown (bottom box) for the 4 elementary conditions (local/global X standard/deviant).

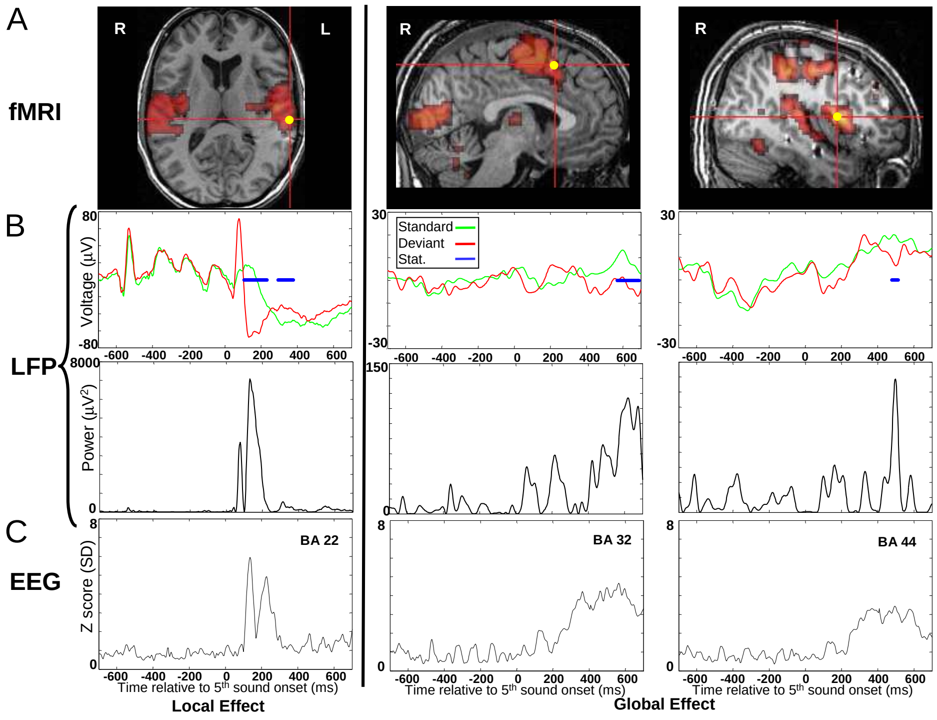

Fig. 3. Brain dynamics of local and global effects. (*A*) Brain fMRI activations are shown for the local (top left) and the global (top right) effects in Talairach's space (horizontal and sagittal slices). For each anatomical view, 1 intracerebral electrode is displayed (yellow disk). (*B*) Averaged LFPs (top) and LFPs power (bottom) are plotted against time for local standard (green) and local deviant (red) trials (left pair), and for global standard (green) and global deviant (red) trials (two right pairs). (*C*) Source activity averaged across the Broadman area including the corresponding intracerebral electrode (BrainStorm software, Matlab) is plotted against time.

global regularity. Note that in this active counting task, no interaction was observed between local and global ERPs effects (see Figs. S1 and S2).

Global Effect Requires Awareness of Stimuli. To evaluate the impact of awareness of the stimuli on these local and global effects, we used 2 manipulations of attention. In Experiment 2, 11 other normal volunteers were instructed to engage in mind-wandering while the sounds were played. The ERP local effect was essentially identical to the one observed in Experiment 1 (see right middle of Fig. 4). In sharp contrast, the global effect decreased dramatically, and no significant effect was observed beyond 400 ms. In Experiment 3, 10 other normal volunteers were asked to detect a visual target in a rapid stream of successive letters, and to neglect the auditory stimuli. Again, the ERP local effect was extremely similar to the 2 preceding experiments (see right lower of Fig. 4). Crucially, violation of the global regularity did not elicit any measurable ERP effect. The disappearance of the global effect coincided with the absence of subjective awareness of the global structure of the task: although each of subjects from the first group (active counting task) reported the presence of locally standard and globally deviant stimuli (AAAAA as rare stimuli), only 3 subjects noticed their presence in the passive group, and none in the visual interference group. In this interference group only 1 subject reported that 1 type of trial was more frequent than any other during each block. Only 1 other subject reported that all blocks began with a series of identical trials. Global deviant trials were never repeated, and reappeared randomly after 2 to 5 global standard trials. A single subject from the interference group could report the existence of this pseudorhythm, whereas it was reported by all subjects belonging to the counting group. A regularity awareness score (RAS) was calculated on these 4 items (see *SI Appendix*) and rated on average at 4/4 in Experiment 1, 2.3/4 in Experiment 2, and 0.4/4 in Experiment 3. Those 3 experiments thus suggest that an ERP signature of global violations is only observed when subjects are conscious of the global regularity structure and of its violations.

Activation of a Global Workspace Network during Global Effect. We then determined which brain areas are activated during the global and local effects (see Fig. 3). In Experiment 4, 9 other normal volunteers were engaged in the active counting task while brain activity was measured using fMRI. Local violation activated the bilateral superior temporal gyri (STG) including primary auditory cortices (see Fig. 3*A*), as observed in previous studies of the fMRI correlates of the auditory MMN (22, 23). In contrast with this anatomically localized pattern, fMRI revealed the activation of a brain-scale distributed network during global violation, including bilateral dorso-lateral prefrontal, anterior cingulate, parietal, temporal and even occipital areas (see Fig. 3*A*).

Intracerebral local field potentials (LFPs) were recorded in 2 epileptic patients implanted for the presurgical mapping of epileptogenic networks. These 2 patients were recorded during the active counting version of the task. Of special interest here, 1 patient had 24 recording sites mostly located in the lateral and mesial parts of the left temporal lobe, 15 of which (62.5%) showed a local effect peaking ≈100–220 ms (see Fig. 3*B*). All 15 electrodes were located in the lateral part of the temporal cortex and most of them within the STG [Broadman Area (BA) 22], in agreement with previous reports of MMN generators (4). Five recording sites (20.8%) showed a global effect in a later temporal window, as observed with scalp ERPs. The second patient had 29 recording sites, mostly implanted in the frontal lobe, 8 (28%) of which showed a significant global effect within a window ranging from 250–600 ms. In particular, LFPs revealed activations of anterior cingulate (BA 32) and dorso-lateral prefrontal (BA 44) cortices during the global effect (see Fig. 3*B*). Interestingly we also observed 3 frontal electrodes showing an early component of the local effect peaking ≈120 ms after sound onset, concurrent to the scalp recorded MMN. This result strengthens the debated proposal of a frontal generator of the MMN, in addition to temporal lobe generators (24, 25).

To assess the congruence of fMRI and LFP measurements, we normalized the patients' brain anatomy in Talairach's space. A strong convergence was observed between fMRI maps, intracerebral recordings and source reconstruction of scalp ERP effects (see Fig. 3 and SOM Table S1). The local effect essentially fitted with the MMN network in auditory cortex, whereas the global effect was subtended by the activity of a global workspace network, particu-

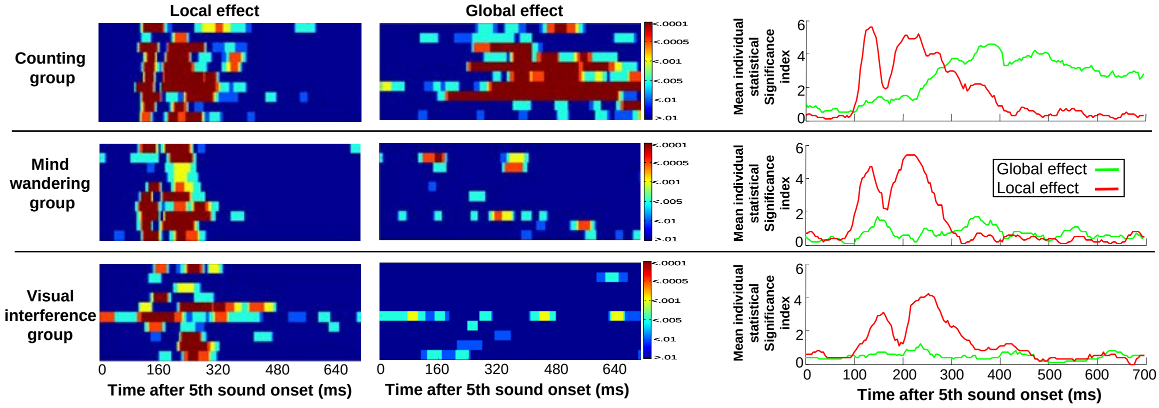

Fig. 4. Local and global effects in individual subjects. (Left) Each horizontal line summarizes an individual subject *t* test statistics (left for the local effect; right for the global effect). Individual statistics are plotted for 10 subjects from each of the Counting (top), Mind-wandering (middle) and Visual interference (bottom) groups. (Right) For each group, we computed a mean individual statistical index by defining linear bins of individual *t* test statistical significance (0 for $P > 0.05$; 1 for $P < 0.05$; 2 for $P < 0.01$; 3 for $P < 0.005$; 4 for $P < 0.001$; 5 for $P < 0.0005$; and 6 for $P < 0.0001$).

larly involving prefrontal cortex, and previously associated with conscious processing (26).

Local and Global Effects Are Detectable in Individual Subjects. We then ran individual analyses of scalp ERP data, to assess the power of our method to detect a global effect in single subjects. For each subject, a *t* test based statistics was computed for each time frame. A local effect was observed in 32/32 (100%) of subjects. In Fig. 4, each of 30 subjects from experiments 1–3 is represented as 2 horizontal lines summarizing respectively the time courses of the local and global effects. We compared the distributions of individual statistics of the local and global effects across the 3 conditions (active, passive, interference) by defining 6 linear bins of significance (from 0 for $P > 0.05$ to 6 for $P < 0.0001$). Bonferroni corrected F tests were performed for each time frame. No difference was observed for the local effect between the 3 groups (see mean values on Fig. 4, right). Concerning the global effect, it was detected in all subjects belonging to the active counting group, whereas 6/11 subjects showed an early global effect in the mind-wandering group (Experiment 2), and only 3/10 subjects showed weak effects in the visual interference group (Experiment 3).

Global Effect Can Be Observed in Some Minimally Conscious Patients. Given that our method detects the presence of a global effect in 100% of subjects performing the active counting task, we used this active task to diagnose conscious processing in 8 noncommunicating patients suffering from disorders of consciousness. Based on the clinical criteria defined by the Aspen group (27), 4 patients were in a minimally conscious state (MCS) and 4 patients were in a vegetative state (VS) (see Table S2 for clinical details). Among the 4 VS patients group, 3 of them had a local effect, but none of them showed a global effect. By contrast, all MCS patients showed a significant local effect and 3 of them demonstrated a clear global effect (see Fig. 5). Interestingly, these 3 patients evolved to a fully conscious state during the following weeks, whereas the MCS patient without a global effect remained in an MCS state by the time of this publication. This last MCS patient without a global effect showed a late (>600 ms) ERP response to the local violations, as

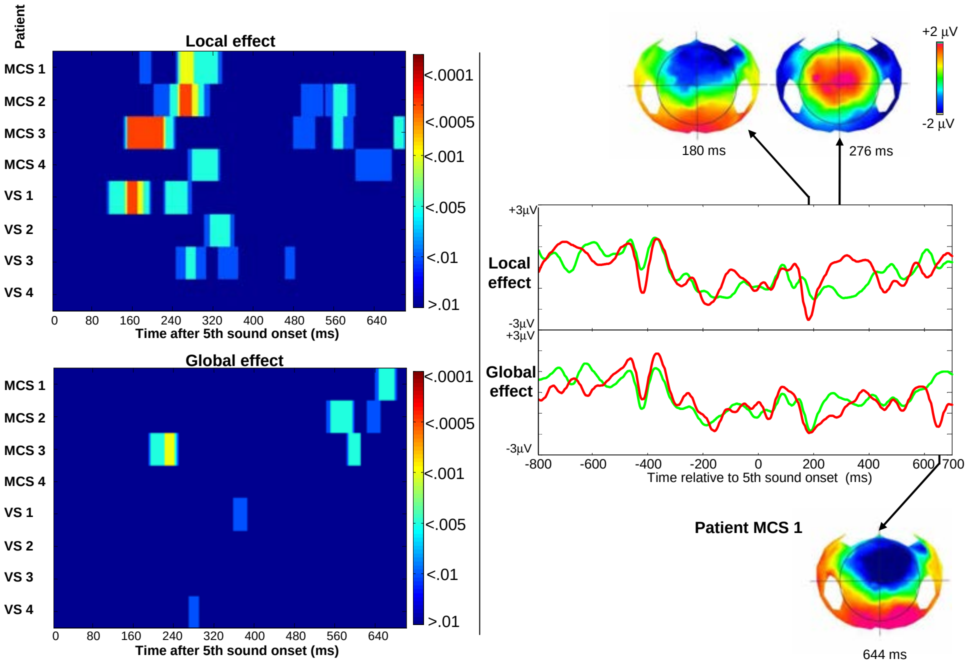

Fig. 5. Local and global effects in noncommunicating patients. Individual statistics are plotted for the 8 noncommunicating patients VS or MCS patients. (Left) Each horizontal line summarizes an individual subject statistics. (Right) Averaged high-density ERPs of the local (top) and global (bottom) effects of patient MCS 1. Voltage scalp topographies are shown for the MMN ≈200 ms (top left), for the local effect vertex-positivity ≈300 ms (top right), and for the global effect (bottom).

observed in 1 normal volunteer from the mind-wandering group and 3 volunteers from the visual interference group. This may suggest that this MCS patient processed consciously the local deviant trials, yet without being able to detect the existence of a global regularity. Fluctuating arousal may have prevented him from actively maintaining task instructions. Two additional MCS patients also showed such a late local effect, which may therefore index partial consciousness together with impaired cognitive abilities.

Discussion

In this study, we designed an auditory paradigm in which 2 embedded levels of auditory regularity are defined, respectively at a local (within trial) and at a global (across trials) time scale.

Auditory Cortex Subtends the Automatic and Nonconscious "Local Effect." Violation of the local regularity elicited 2 major ERP effects within an early 130–300 ms temporal window: first a typical MMN, followed by a central positivity with simultaneously bilateral occipito-temporal negativities. These 2 effects are highly suggestive of an automatic, nonconscious, and encapsulated mode of processing. Indeed, these local effects remained largely unchanged whether subjects had to count the number of global violations (experiment 1), to mind-wander (experiment 2), or to engage their attention in a competing RSVP task (experiment 3). Moreover, combination of fMRI maps, ERP source estimations, and intracranial recordings demonstrated that these local effects were not only local in time, but also in space: they mostly originated from a restricted anatomical network, the epicenters of which are bilateral superior temporal auditory cortices, and at a smaller extent, probable frontal generators. Finally, our finding that these local effects could still be observed in some patients lacking behavioral evidence of conscious processing (VS patients) strengthens their automaticity. This subset of results strongly suggests that the existence of an early ERP local effect in a noncommunicating patient reflects the preserved nonconscious integration of auditory environment, as previously observed for the MMN in more basic paradigms (13, 15, 16, 27), but need not imply conscious perception. Interestingly however, 3 MCS patients, including the patient without significant ERP global effect, showed local effects with unusually late components. These late local effects, less frequently observed in the control subjects of our 3 experiments, may index the conscious processing of local regularities. Indeed, MCS patients are probably more prone to miss the global regularity of the auditory stimuli, because of fluctuations in their level of arousal and to difficulties in decoding and actively maintaining task instructions. As a consequence, they may be more attracted than controls to consciously process violations of the local regularities. If correct, this hypothesis would suggest that the late component (> 400 ms) of the ERP local effect could index conscious processing of local violations. One test of this hypothesis might consist in recording normal controls while they perform an active task focusing on violation of local regularities.

A Global Workspace Network Subtends the Conscious "Global Effect." Taken together, our results strongly suggest that the reaction of the brain to violations of global regularities can serve as a marker of conscious processing of the auditory environment. However, being merely awake and aware is not enough to elicit a global effect. In conscious controls, a global effect was present only when subjects were conscious of the global regularity violations. When we interfered with this specific conscious content by mind-wandering instructions or a visual interference task, the global effect vanished in parallel with conscious reportability of the global regularity. Anatomically, brain regions activated during the global effect spanned over a brain-scale cortical network including prefrontal, cingulate, parietal and temporal regions. This network fits nicely with our previous theoretical proposal that conscious processing is subtended by the coherent activity of a global workspace network (26, 28), and not by the transient and isolated activation of any cortical region, including prefrontal cortex, as recently observed (29–32). Additionally, the absence of a global effect in the VS patients indicates that our test is not a simple measure of vigilance, but a measure of subjective conscious contents.

A Potentially Specific Clinical Tool. Our converging set of ERP, fMRI, and intracerebral recordings demonstrates that the local-global paradigm constitutes a promising clinical tool to diagnose conscious processing. Even a single vertex electrode, placed at bedside, followed by a few minutes of auditory testing, might suffice to identify conscious patients who are aware of the global auditory regularities. When it is observed, this global effect seems to be a specific diagnostic marker of consciousness. Note however, that the reverse is not true: the absence of a global effect does not exclude the possibility of conscious processing, given that it is absent in distracted or mind-wandering conscious controls who could not report the global rule. One should keep in mind that a patient may still be conscious but unable to understand the instructions, to actively maintain attention, or to deploy working memory processes necessary to perform the task. In such cases, we tentatively propose that a late local effect may still be suggestive of conscious processing of the local variations in a subject who could not extract the global auditory rule. When the global effect is absent, and only an early and transient local effect is observed, interpretation must be cautious. This pattern may signal nonconscious processing, as previously observed in comatose patients (13–15) and in vegetative state patients (16, 17), but also a patient who is aware but not attending. Indeed, all functional measures of conscious processing are also subject to variations of arousal, attention, and task performance (33). Furthermore, there is no clear consensus concerning the definition of consciousness, and other theoretical models may propose that a form of "phenomenal consciousness" (34), or of "unattended consciousness" (35, 36) still accompanies the early local effect.

Overall, our study confirms the relevance of using active tasks even in noncommunicating patients, to probe their cognitive abilities with neurophysiological methods (28–30). One may consider it urgent to integrate some of these measures into the clinical assessment of the conscious state in noncommunicating patients in whom a mere behavioral assessment of cognitive abilities is of limited power.

Materials and Methods

Subject and Patients. Experiments were approved by the Ethical Committee of the Salpêtrière hospital. The 41 normal controls (mean age = 27.0 ± 3.0; sex-ratio = 0.9) tested (32 with scalp ERPs + 9 with fMRI), and the 2 epileptic patients gave written informed consent. Three scalp ERP subjects were not included in the analysis because of excessive movement artefacts. Concerning the 8 noncommunicating patients (see Table 2), scalp ERP recordings were done after families gave informed consent. In addition to clinical examination, we used the French version (established by Laureys in 2004) of the revised Coma Recovery Scale (CRS-R) by Kalmar and Giacino (37). Note also that the local effect had a direct clinical impact by probing the presence of a MMN. This bedside neurophysiological test is a routine exploration with both a functional diagnosis and an outcome prognosis values (15, 27).

Auditory Stimulations. Series of 5 complex 50-ms-duration sounds were presented via headphones with an intensity of 70 dB and 150 ms SOA between sounds. Each sound was composed of 3 sinusoidal tones (either 350, 700, and 1400 Hz, hereafter sound A; or 500 Hz, 1000 Hz, and 2000 Hz, hereafter sound B). All tones were prepared with 7-ms rise and 7-ms fall times. Four different series of sounds were used, the first 2 using the same 5 sounds (AAAAA or BBBBB); and the second with the final sound swapped (either AAAAB or BBBBA). Series of sounds were separated by a variable interval of 1350 to 1650 ms (50-ms steps). All subjects heard 8 blocks (3–4 min duration), in randomized order for each subject (each of the 4 possible block types was presented twice). The blocks were designed to contain the sound series with a different sound in the end, either as an infrequent stimulus (block type a: 80% AAAAA/20% AAAAB; block type b: 80% BBBBB/20% BBBBA); or as a frequent stimulus (block type c: 80% AAAAB/20% AAAAA; block type d: 80% BBBBA/20% BBBBB). All block types presented a local regularity (the fifth sound could be different or identical to previous sounds) and a global regularity (one of the series of sounds was less frequent than the other). Each block started with 20–30 frequent series of sounds to establish the global regularity before the first infrequent stimulus arrival. In each block the number of infrequent trials varied between 22 and 30. For the 'mind-wandering' condition, subjects were instructed as follows: ''During the next 30 min different sounds will be played by the headphones for successive periods of approximately 3 minutes. You don't need to pay attention to these sounds. Please close your eyes, and let yourself mind-wander.''

The interference group (experiment 3) performed a continuous letter detection task during each block of auditory stimuli. The visual task began 5–10 seconds before the onset of the series of sounds and finished 5–10 seconds later. The visual stimuli were letters appearing at the center of the screen. The visual stimuli were cyan, dark yellow, black, magenta, or red characters rendered on a light gray background. There were 12 different letters and, thus, 24 possible stimuli (majuscule or minuscule letters) in each block. The uppercase letters A, D, T, and X were used twice each as targets, for a total of 8 blocks. The letters subtended 1° of visual angle horizontally and vertically. Subjects had to press the spacebar to targets in each block as fast as they could. The maximum time for presentation and response was 1,000 ms. After each button press the response time appeared on screen as feedback. No causal relation prevailed between visual and auditory stimuli. All stimuli were presented using Eprime v1.1 (Psychology Software Tools Inc.).

For the fMRI experiments, the same experimental set-up (structure and timing) was used, with an additional silent baseline period (19.2 seconds) at the beginning and at the end of each of the 8 blocks.

High-Density Scalp ERPs. ERPs were sampled at 250 Hz with a 128-electrode geodesic sensor net (EGI) referenced to the vertex (for experiment 3 and for the 8 patients, a 256-electrode geodesic sensor net was used). We rejected voltages exceeding $\pm 200~\mu$V, transients exceeding $\pm 100~\mu$V, or electro-oculogram activity exceeding $\pm 70~\mu$V. Trials were then segmented from −200 ms to + 1300 ms relative to the onset of the first sound. Bad channels were interpolated. Trials with >25 bad channels were rejected. The remaining trials were averaged in synchrony with stimulus onset, digitally transformed to an average reference, band-pass filtered (0.5–20 Hz) and corrected for baseline over a 200-ms window before stimulus onset. For the 8 patients recorded in the noisy environment of the intensive care unit, we used a baseline correction over the 800-ms window before stimulus onset. All those processing stages were performed in the EGI Waveform Tools Package. Matlab 7.0 scripts were used to compute sample-by-sample paired t tests with a triple criterion of: $P < 0.01$ for at least 10 consecutive samples on 10 electrodes.

For individual subject statistics, unpaired t tests were calculated for each time sample on individual trials. An effect was considered significant if it satisfied a triple-threshold: *t* test P value <0.01 on a minimum of 5 consecutive samples, on a minimum of 10 electrodes (20 for the 256 channels net). To further assess the reliability of our test, we visualized for each time-sample the significance of the local and global effects using a 5-levels *P* value color scale (see Fig. 4), ranging from 0.01, 0.005, 0.001, 0.0005, and 0.0001.

For source estimation, cortical current source density mapping was obtained using a distributed model consisting in 10,000 current dipoles. Dipole locations and orientations were constrained to the cortical mantle of a generic brain model built from the standard brain of the Montreal Neurological Institute using the BrainSuite software package. This head model was then warped to the standard geometry of the sensor net. The warping procedure and all subsequent source analysis, and statistical estimation of the Z-scores relative to the baseline (−200 ms to + 600 ms) were processed with the BrainStorm software package (http://neurimage.usc.edu/brainstorm). EEG forward modeling was computed with an extension to EEG of the overlapping-spheres analytical model. Cortical current maps were computed from the EEG time series using a linear inverse estimator [weighted minimum-norm current estimate or WMNE, see (38) for review].

Local Field Potentials and fMRI Methods. See *SI Text*.

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Probing consciousness with event-related potentials in the vegetative state

F. Faugeras, MD
B. Rohaut, MD
N. Weiss, MD
T.A. Bekinschtein, PhD
D. Galanaud, MD, PhD
L. Puybasset, MD, PhD
F. Bolgert, MD
C. Sergent, PhD
L. Cohen, MD, PhD
S. Dehaene, PhD
L. Naccache, MD, PhD

Address correspondence and reprint requests to Dr. L. Naccache, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Neurophysiology, Paris, France
lionel.naccache@psl.aphp.fr

ABSTRACT

Objective: Probing consciousness in noncommunicating patients is a major medical and neuroscientific challenge. While standardized and expert behavioral assessment of patients constitutes a mandatory step, this clinical evaluation stage is often difficult and doubtful, and calls for complementary measures which may overcome its inherent limitations. Several functional brain imaging methods are currently being developed within this perspective, including fMRI and cognitive event-related potentials (ERPs). We recently designed an original rule extraction ERP test that is positive only in subjects who are conscious of the long-term regularity of auditory stimuli.

Methods: In the present work, we report the results of this test in a population of 22 patients who met clinical criteria for vegetative state.

Results: We identified 2 patients showing this neural signature of consciousness. Interestingly, these 2 patients showed unequivocal clinical signs of consciousness within the 3 to 4 days following ERP recording.

Conclusions: Taken together, these results strengthen the relevance of bedside neurophysiological tools to improve diagnosis of consciousness in noncommunicating patients. *Neurology*® 2011; 77:264–268

GLOSSARY

CRS-R = Coma Recovery Scale–Revised; **ERP** = event-related potential; **MCS** = minimally conscious state; **VS** = vegetative state.

Evaluating abnormal states of consciousness may be extremely challenging when relying only on the clinical examination alone. EEG-based paradigms have many advantages over fMRI for monitoring patients with altered consciousness because of 1) the millisecond-range resolution, 2) the low cost and noninvasiveness, 3) the ability to monitor at the bedside, and 4) the possibility of designing dedicated systems for clinical use.

We recently designed a new test of consciousness using high-density scalp EEG in an auditory odd-ball paradigm.[1] This test capitalizes on 2 properties which are specific to conscious processing[2–4]: one has to be conscious of a mental representation to actively maintain it in working memory, and to use it strategically. Our test evaluates cerebral responses to violations of temporal regularities. Short-interval violations due to the unexpected occurrence of a single deviant sound among a repeated train of standard sounds led to an early and automatic response in auditory cortex, the mismatch negativity ERP component. Moreover, long-term violations, defined as the presentation of a rare and unexpected series of 5 sounds, led to a late and spatially distributed response that was present only when subjects were attentive and aware of the auditory rule and of its violations (P3b component). Our observations showed that this

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From the Departments of Neurophysiology (F.F., B.R., L.N.), Neurology (N.W., F.B., L.C., L.N.), and Neuroradiology (D.G.), and Neurosurgical Intensive Care Unit (L.P.), AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Paris, France; MRC Cognition and Brain Sciences Unit (T.A.B.), Cambridge, UK; INSERM (F.F., B.R., D.G., C.S., L.C., L.N.), ICM Research Center, UMRS 975, Paris; INSERM-CEA Cognitive Neuroimaging Unit/CEA/SAC/DSV/DRM/Neurospin Center (S.D.), Gif/Yvette Cedex; Institut du Cerveau et de la Moëlle Épinière (F.F., B.R., D.G., C.S., L.C., L.N.), Paris; and University Paris 6 (L.P., L.C., L.N.), Faculté de Médecine Pitié-Salpêtrière, Paris, France.

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rule violation effect is a specific signature of conscious processing, although it can be absent in conscious subjects unaware of long-term auditory regularities.

In this work, we explored the relevance of this rule violation effect test in 31 patients who were in vegetative states of various chronicity. Our main objective was to assess the added value of our test in patients in whom detailed clinical examination and Coma Recovery Scale–Revised (CRS-R) scoring failed to detect any reliable evidence of consciousness. The second objective of this study was to explore the prognostic value of the test by following each of these patients, and to correlate the ERP test with early and late outcomes.

METHODS

Standard protocol approvals, registrations, and patient consents. This study has been approved by the ethical committee of the Salpêtrière Hospital (Paris, France).

Controls. Ten controls were recorded (age 20.3 ± 0.7 years; sex ratio [M/F] 2.3). Data from 2 subjects were discarded due to excessive movement artifacts.

Patients. We report here all recordings of patients in vegetative state (VS) from November 2008 to February 2010. Patients with clinical criteria of VS, irrespective of delay from

Table **Patients' characteristics and outcomes**

Patient no.	Age, y	Sex	Etiology	Lesion site	Delay, days	CRS-R Total	CRS-R Subscores	ERP	Outcome <7 d	Outcome >6 mo
1	62	F	ADEM	Diffuse white matter hyperintensities	25	1	0/0/0/0/0/1	+	MCS	MCS
2	47	F	Anoxia	—	54	3	1/0/1/0/0/1	–	Dead	Dead
3	48	F	Anoxia	Diffuse gray and white matter hyperintensities	14	3	0/0/1/1/0/1	–	VS	Dead
4	61	M	ICH	IVH + diffuse white matter hyperintensities	25	3	0/0/0/1/0/2	–	Dead	Dead
5	29	F	Anoxia	Diffuse brain atrophy	85	4	1/0/1/1/0/1	–	VS	Dead
6	65	F	Anoxia	Diffuse cortical and basal ganglia hyperintensities	20	4	1/0/1/1/0/1	–	VS	VS
7	74	F	Anoxia	Diffuse brain atrophy	610	5	1/1/1/1/0/1	–	VS	Dead
8	44	M	ICH	Left cerebellar hematoma + IVH	42	5	1/0/1/1/0/2	–	VS	MCS
9	67	M	ICH	Right frontal hematoma + IVH	25	5	1/1/1/1/0/1	–	VS	Dead
10	41	M	ICH	Left frontoparietal hematoma + ICA aneurysm + left MCA and ACA vasospasm	350	5	1/0/1/2/0/1	–	VS	VS
11	46	M	Stroke	Bilateral mesencephalic + cerebellum + thalamic + occipital stroke	89	5	1/0/1/1/0/2	–	VS	Dead
12	51	M	TBI	Right convexity SDH + bilateral hemorrhagic cortical contusions	15	5	1/1/1/1/0/1	+	MCS	Dead[a]
13	43	F	TBI	Severe brain atrophy (cortical cavitations)	2,555	5	1/0/1/1/0/2	–	VS	VS
14	22	M	Anoxia	Diffuse cortical and basal ganglia hyperintensities	16	5	1/0/1/1/0/2	–	VS	CS
15	40	M	TBI	Right temporofrontal EH + left hemispheric SDH	62	6	1/1/2/1/0/1	–	VS	Dead
16	76	M	Anoxia	Diffuse leukoencephalopathy	25	6	1/1/2/1/0/1	–	MCS	Dead
17	70	F	ICH	Left frontal hematoma + ACoA aneurysm + left MCA and ACA vasospasm	17	6	1/1/2/1/0/1	–	Dead	Dead
18	39	M	ICH	ICA aneurysm + left caudate hematoma	37	6	1/1/1/1/0/2	–	VS	CS
19	62	M	ICH	ACoA aneurysm + interhemispheric hematoma + IVH	19	7	1/1/2/1/0/2	–	VS	CS
20	29	M	TBI	Right frontoparietal SDH + IVH	33	7	2/1/2/1/0/1	–	VS	CS
21	45	M	Anoxia	Mesencephalic + right hemispheric cerebellar hyperintensities	19	7	2/1/1/1/0/2	–	VS	Dead
22	76	F	Anoxia	Diffuse brain atrophy	46	8	2/1/2/2/0/1	–	MCS	CS

Abbreviations: ACoA = anterior communicating artery; CRS-R = Coma Recovery Scale–Revised; CS = conscious state; EH = extradural hematoma; ERP = event-related potential; ICA = internal carotid artery; IVH = intraventricular hemorrhage; MCA = middle cerebral artery; MCS = minimally conscious state; SAH = subarachnoid hemorrhage; SDH = subdural hematoma; UA = unresponsive awake state (criteria of vegetative state irrespectively of delay); VS = vegetative state.

[a] The patient died from a fatal hemorrhage recurrence on day 34.

disease onset (both early and longstanding states), were included. Patients were recorded without sedation since at least 24 hours. Among the 31 recordings 9 were discarded after evaluation of EEG quality (appendix e-1 on the *Neurology*® Web site at www.neurology.org). This high rate of rejection (29%) reveals one of the limits of this technique. The 22 valid datasets included 13 men and 9 women, aged from 22 to 76 years (mean 51.7 years), with both early and late recordings (mean 190 days; median 29 days; SD 546 days; earliest 14 days; latest 2,555 days; table).

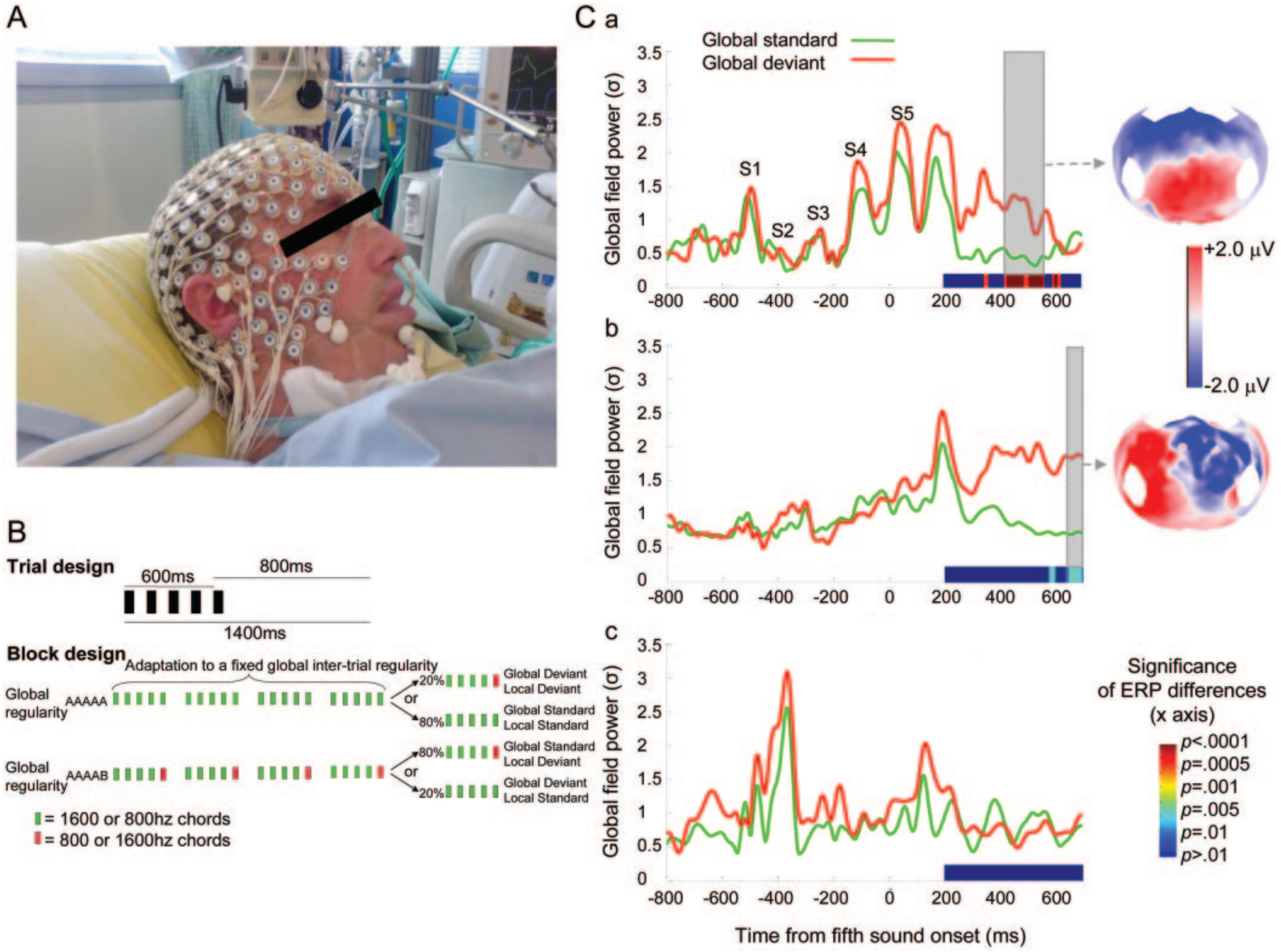
Behavior. The clinical definition of VS was based on the French version of the CRS-R scale.[5] It was carried out after careful neurologic examination by trained neurologists (F.F., L.N.), immediately before ERP recording.

Stimulation and ERPs. We used our previously published auditory protocol while recording high-density scalp EEG (EGI, Eugene, OR). See reference[1] and appendix e-1 for details.

RESULTS A rule violation ERP effect was present in each of the 8 controls (100%) within the 300–700 msec temporal window after the onset of the fifth sound, replicating our previous findings (see control group 1 in reference[1]). Among the 22 patients, 2 (9%) showed a significant effect (figure). None of the remaining 20 patients was deaf, and early cortical responses to the tones could be identified on all ERP recordings, thus discarding a trivial interpretation of the absence of rule violation effect.

One of the 2 patients was a 62-year-old woman with a severe form of acute disseminated encephalomyelitis following a spontaneously resolving flu-like episode. MRI showed extensive bilateral hemispheric hyperintensities on fluid-attenuated inversion recovery images, with gadolinium enhancement on T1-

Figure **Test design and illustration of bedside recording in intensive care unit (ICU)**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(A) Bedside recording in ICU. Photography of the recording setting in a patient in the ICU (with the patient's permission). Installation of the net and EEG calibration requires about 15 minutes. Earphones are then applied, task instruction delivered, and EEG recording starts. (B) Auditory paradigm. On each trial 5 sounds were presented. Each block started with 20–30 frequent series of sounds to establish the long-term regularity before delivering the first infrequent rule deviant stimulus. (C) Three representative results. Global field power of rule standard (green) and rule deviant (red) trials are plotted for one conscious control subject (C.a), for a patient with a rule violation effect (C.b), and for a patient without rule violation effect (C.c). Early peaks to each of the 5 sounds (S1 to S5) are indicated for the control subject. Statistical significance of event-related potential (ERP) differences within the time window of the rule violation effect is indicated by a color code on the X axis. Voltage topography maps averaged across time windows of significant ERP effects are displayed on the right. Panel C is reprinted from Bekinschtein et al.[1]

weighted sequence. She was recorded 25 days after disease onset. Neurologic examination immediately before ERP recording showed preserved brainstem reflexes, with slight anisocoria (right $<$ left). Babinski and Hoffmann signs were observed on the left side. All tendon reflexes were present. Eye-opening was systematically obtained under auditory or nociceptive stimulation. However, even when arousal was stimulated, no behavioral sign of consciousness could be obtained (CRS-R = 1/23).

The second patient with a positive ERP test was a 51-year-old man who had a severe traumatic brain injury with a massive acute right-hemispheric subdural hematoma which required surgical treatment. MRI then revealed additional hemorrhagic cortical contusions located in both occipital and frontal areas, and in the left mesial temporal lobe. He was recorded 15 days after trauma. Neurologic examination immediately before ERP recording showed preserved brainstem reflexes, with a slow stereotyped flexion response to nociceptive stimulation. A left Babinski sign was present, and all tendon reflexes were present. Eye-opening was systematically obtained under auditory or nociceptive stimulation, and CRS-R reached 5/23.

Both patients reached criteria of minimally conscious state (MCS) 3 and 4 days after ERP recording, respectively. By contrast, in the 20 remaining patients with a negative result, early recovery of consciousness was observed in only 2 cases within the first week ($\chi2 = 9.90$, $p = 0.002$; Fisher exact test: $p = 0.026$), indicating that the global effect was significantly predictive of overt consciousness recovery. When studying outcome within a longer time frame ($>$6 months), 7/20 initially VS patients without ERP effect reached either an MCS or conscious state ($\chi2$ test = 3.18, unilateral $p = 0.037$).

DISCUSSION A rule violation effect was observed in 2 patients who met clinical criteria of VS, suggesting that they consciously identified rule deviants. The relative weakness of their effect may correspond to fluctuations of consciousness or to partial execution of the task (e.g., conscious identification of targets without counting). In any case, as shown previously,[1] the mere identification of rule deviant trials requires conscious processing of the stimuli, while nonconscious P300/N400-like ERP responses have been reported with simpler paradigms in controls and patients.[6–9] Therefore, the positivity of this ERP test is a strong argument to correct the clinical diagnosis in these 2 patients, and to classify them as conscious in spite of the negative behavioral assessment. In both patients, the negativity of clinical examination and of CRS scoring could not be explained by motor impairments. These 2 cases are reminiscent of recent reports of the few patients clinically assessed as VS who showed evidence of consciousness in active fMRI paradigms.[10,11]

Our test, however, presents several limitations: the high rate of data rejection is inherent to EEG recording in awake and nonsedated patients. Moreover, our test lacks sensitivity in as much as it requires the patient not only to be conscious, but also to understand task instructions, to keep them in working memory, to continuously keep attention focused on the stimuli, and to mentally count global deviants.

The second objective of our study was to explore value of the ERP global effect for the prognosis of patients in VS. Interestingly, in terms of consciousness, the early outcome was much better in patients with a rule violation effect than in those lacking it. This differential outcome was less pronounced on a longer time scale. This is compatible with our proposal that the rule violation effect is a neural signature of consciousness per se rather than a predictor of consciousness recovery. Long-term ($\geq$2 years) follow-up will be addressed in a dedicated study.

The auditory rule violation ERP test can be used to probe consciousness, and its positivity in patients who meet clinical criteria of VS therefore questions the clinical diagnosis.

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DISCLOSURE

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Editor's Note to Authors and Readers: Levels of Evidence coming to *Neurology*®

Effective January 15, 2009, authors submitting Articles or Clinical/Scientific Notes to *Neurology*® that report on clinical therapeutic studies must state the study type, the primary research question(s), and the classification of level of evidence assigned to each question based on the classification scheme requirements shown below (left). While the authors will initially assign a level of evidence, the final level will be adjudicated by an independent team prior to publication. Ultimately, these levels can be translated into classes of recommendations for clinical care, as shown below (right). For more information, please access the articles and the editorial on the use of classification of levels of evidence published in *Neurology*.[1-3]

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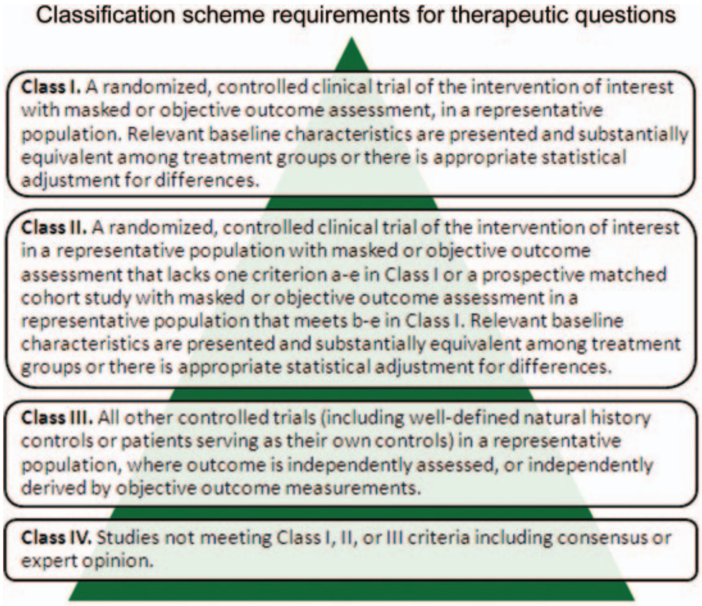


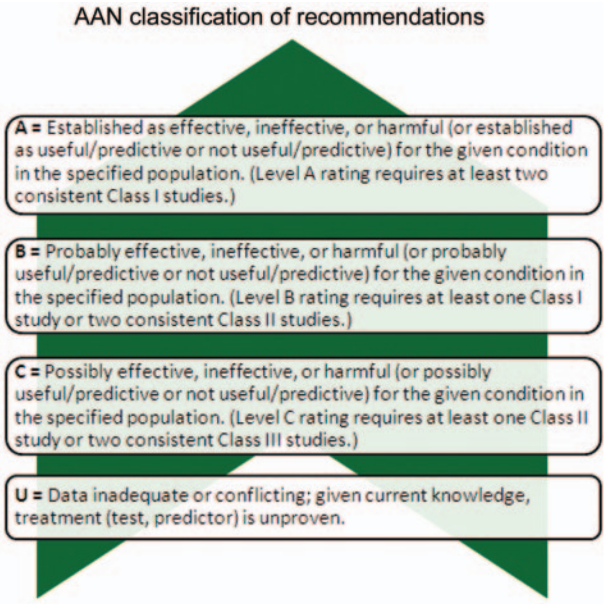
Classification scheme requirements for therapeutic questions

Class I. A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II. A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a-e in Class I or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e in Class I. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III. All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurements.

Class IV. Studies not meeting Class I, II, or III criteria including consensus or expert opinion.



AAN classification of recommendations

A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)

B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

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Event related potentials elicited by violations of auditory regularities in patients with impaired consciousness

Frédéric Faugeras[a,e,i], Benjamin Rohaut[a,e,i], Nicolas Weiss[b], Tristan Bekinschtein[g], Damien Galanaud[d,e,i], Louis Puybasset[c,h], Francis Bolgert[b], Claire Sergent[e,i], Laurent Cohen[b,e,h,i], Stanislas Dehaene[f], Lionel Naccache[a,b,e,h,i,*]

[a] AP-HP, Groupe hospitalier Pitié-Salpêtrière, Department of Neurophysiology, Paris, France
[b] AP-HP, Groupe hospitalier Pitié-Salpêtrière, Department of Neurology, Paris, France
[c] AP-HP, Groupe hospitalier Pitié-Salpêtrière, Department of Neurosurgical Intensive Care Unit, Paris, France
[d] AP-HP, Groupe hospitalier Pitié-Salpêtrière, Department of Neuroradiology, Paris, France
[e] INSERM, ICM Research Center, UMRS 975, Paris, France
[f] INSERM-CEA Cognitive Neuroimaging Unit | CEA/SAC/DSV/DRM/Neurospin Center, Gif/Yvette cedex, France
[g] MRC-Cognition and Brain Sciences Unit, Cambridge, UK
[h] University Paris 6, Faculté de Médecine Pitié-Salpêtrière, Paris, France
[i] Institut du Cerveau et de la Moëlle épinière, Paris, France

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ABSTRACT

Improving our ability to detect conscious processing in non communicating patients remains a major goal of clinical cognitive neurosciences. In this perspective, several functional brain imaging tools are currently under development. Bedside cognitive event-related potentials (ERPs) derived from the EEG signal are a good candidate to explore consciousness in these patients because: (1) they have an optimal time resolution within the millisecond range able to monitor the stream of consciousness, (2) they are fully non-invasive and relatively cheap, (3) they can be recorded continuously on dedicated individual systems to monitor consciousness and to communicate with patients, (4) and they can be used to enrich patients' autonomy through brain–computer interfaces. We recently designed an original auditory rule extraction ERP test that evaluates cerebral responses to violations of temporal regularities that are either local in time or global across several seconds. Local violations led to an early response in auditory cortex, independent of attention or the presence of a concurrent visual task, while global violations led to a late and spatially distributed response that was only present when subjects were attentive and aware of the violations. In the present work, we report the results of this test in 65 successive recordings obtained at bedside from 49 non-communicating patients affected with various acute or chronic neurological disorders. At the individual level, we confirm the high specificity of the 'global effect': only conscious patients presented this proposed neural signature of conscious processing. Here, we also describe in details the respective neural responses elicited by violations of local and global auditory regularities, and we report two additional ERP effects related to stimuli expectancy and to task learning, and we discuss their relations to consciousness.

1. Introduction

"*Is he/she conscious*?" Far from being a purely philosophical abyssal issue, this question is a daily interrogation for the caregivers and health professionals of acute or chronic non-communicating patients. Answers to this question are crucial to optimize the medical management of those patients, to specify the amount of efforts devoted to communicate with them, and to provide robust objective landmarks to the caregivers and close relatives of the patients in these extremely difficult situations where irrepressible emotions, subjective feelings and interpretative beliefs may be misleading and insufficient to guide medical strategy.

For many years, clinical examination and behavioral observation constituted the single approach to diagnose consciousness (Plum & Posner, 1972). Consciousness is clinically defined in relation to the diverse neurological conditions where it is impaired or absent. Major principles can be derived from clinical neurology.

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* Corresponding author at: AP-HP, Groupe hospitalier Pitié-Salpêtrière, Department of Neurophysiology, Paris, France.
E-mail addresses: lionel.naccache@psl.aphp.fr, lionel.naccache@gmail.com (L. Naccache).

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1.1. Clinical markers of consciousness

1.1.1. Consciousness requires wakefulness: the case of comatose states

First, a necessary but insufficient physiological condition to consciousness is wakefulness, that is to say the presence of waking periods during which the patient keeps his eyes open independently of external stimulations. Wakefulness is impaired in comatose states, in general anesthesia or in deep sleep stages in which patients are not conscious (Laureys, Owen, & Schiff, 2004). The neural bases of wakefulness mostly involve complex brainstem and thalamic networks often regrouped under the generic term of ascending reticular activating system (ARAS) (see Moruzzi & Magoun, 1949; Parvizi & Damasio, 2001 for a recent review).

1.1.2. Consciousness is not wakefulness: the case of vegetative states

A more subtle alteration of consciousness is the vegetative state (VS), which is characterized by preserved wakefulness (Jennett & Plum, 1972) – even if circadian rhythms may not be strictly normal (Bekinschtein, Golombek, Simonetta, Coleman, & Manes, 2009) – in the absence of any purposeful behavior and of any sign of intentional reactions to the external environment. Note that VS is, by definition, a clinical syndrome and not a specific condition. For this reason, and in order to avoid too radical interpretations of patient's cognitive state only based on behavioral observations, a group of experts recently proposed the 'Unresponsive Wakefulness Syndrome' expression to describe VS (Laureys et al., 2010).

The mere existence of VS demonstrates that wakefulness and consciousness can be dissociated, and therefore that they cannot be identified one with another (Bernat, 2006). While VS can have a highly variable duration, from several days to a whole lifetime, other neurological situations can be described as 'transient VS': during complex partial epileptic seizures or during "petit mal absence" seizures for instance, a comparable dissociation between consciousness and wakefulness occurs, but on a much shorter timescale, usually from a few seconds to several minutes (Blumenfeld & Taylor, 2003).

1.1.3. Transitions between VS and consciousness: the case of minimally conscious states (MCS)

Neurological observations revealed that many patients presented fluctuating states which could be identified neither as VS nor conscious states. These transitional states have recently been regrouped under the concept of minimally conscious states (MCS, Giacino et al., 2002). The behavioral distinction between VS and MCS requires an expertise in clinical assessment and can be based on the use of a dedicated scale: the revised version of the Coma Recovery Scale (CRS-R, see Kalmar & Giacino, 2005, adapted in many languages including French, Schnakers, Majerus, et al., 2008). For instance, while VS patients can show fast and transient saccadic responses to moving visual targets, the presence of sustained and reproducible visual pursuit is an index of MCS. Note that a recent work showed that the use of EMG signal in active motor paradigms is more sensitive than mere clinical examination of overt movements (Bekinschtein, Coleman, Niklison, Pickard, & Manes, 2008).

1.1.4. Motor neurological examination is a prerequisite: pitfalls of locked-in syndromes

Prior to consciousness assessment, a detailed clinical checking of the functionality of motor pathways is absolutely necessary, as demonstrated by various clinical conditions in which a paralyzed but conscious patient can be misclassified as unconscious. "Locked in syndrome" usually secondary to brainstem strokes in the paramedian protuberance (Laureys et al., 2005), but also related conditions such as severe Guillain–Barré polyradiculoneuritis or severe amyotrophic lateral sclerosis are typical illustrations of this point.

1.1.5. Covert cognitive impairments may underestimate consciousness

Note also that the presence of massive cognitive impairments may be difficult to detect and may lead to an underestimation of consciousness. For instance, a non-communicating patient affected by a global aphasia (e.g.: massive left hemispheric lesion) will probably not demonstrate any adapted behavior even to basic verbal instructions. Similarly, massive impairments in anterograde memory, in working memory or executive functions can lead to an underestimation of the consciousness status.

In the light of these fundamental neurological principles, it is clear that purely behavioral observations have limited sensitivity, and only constitute indirect evidence of conscious processes. In some cases, the categorization of a patient as vegetative or minimally conscious is far from obvious. Thus, in many daily clinical situations, the inaugural question of this article is left unanswered: "*Is he/she conscious*?"

1.2. Markers of consciousness derived from cognitive neuroscience

A complementary approach to clinical neurology originates from cognitive neurosciences of consciousness. Although the issue remains debated, two decades of experimental and theoretical works have led to the characterization of psychological and neurophysiological attributes that may be unique to conscious processing (Seth, Dienes, Cleeremans, Overgaard, & Pessoa, 2008). Many cognitive processes may occur unconsciously both in conscious subjects (Dehaene, Changeux, Naccache, Sackur, & Sergent, 2006; Kouider & Dehaene, 2007), in visual neglect patients or related patients (Driver & Mattingley, 1998; Naccache, 2008), and in non conscious patients (Laureys, 2005; Owen et al., 2005), reaching such complex levels as abstract semantics, phonological or emotional processing. Still, three properties seem to be exclusively associated with conscious processing of reportable mental contents (Dehaene & Naccache, 2001): (i) active maintenance of mental representations in working memory; (ii) strategical processing; and (iii) spontaneous intentional behavior. Similarly, while unconscious processing may engage multiple isolated cortical areas, neural signatures of conscious processing are defined by late and long-lasting brain activations that mobilize long-distance coherent thalamo-cortical networks, particularly involving bilateral prefrontal, cingulate and parietal areas (Dehaene et al., 2006; Gaillard et al., 2009).

On the basis of these studies, original experimental paradigms can therefore be designed in order to improve our ability to diagnose consciousness in non-communicating patients, beyond clinical evaluations. For instance, at the behavioral level, Bekinschtein, Shalom, et al. (2009) capitalized on the working memory property mentioned above, and used an eyeblink conditioning paradigm in which a tone stimulus can be paired with an air-puff delivered on the cornea. Delay conditioning – where the conditioned stimulus and the unconditioned air-puff overlap in time – does not require conscious processing of the stimuli. In contrast, trace conditioning where a temporal gap is inserted between the two stimuli seems to require conscious processing in working memory (Clark & Squire, 1998). Interestingly, they showed that some clinically defined VS patients were able to demonstrate both conditioning and trace conditionings. Functional brain-imaging approaches are also emerging (Coleman et al., 2009). For instance, Owen et al. (2006) probed with fMRI the active maintenance of task-instructed cognitive tasks, such the ability to perform motor or spatial imagery tasks for a extended duration of 30 s. Using this approach on 54 patients, they could identify 5 patients able to willfully modulate their brain activity (Monti et al., 2010). Among these 5 patients, two were clinically classified as VS. In one clinically MCS patient, fMRI could be used to define an arbitrary code and communicate a single bit of information (a yes/no answer), while such a communication was not possible behaviorally.

In parallel to such fMRI experiments, EEG paradigms may constitute a highly promising research direction for at least two reasons. First, EEG is a time-resolved tool able to sample brain activity at the millisecond scale. This offers a unique opportunity to monitor the flow of consciousness and eventually to interact with the patient in real-time. Second, given that EEG is a non-invasive technique, has a relatively low-cost and can be recorded at bedside, one may ultimately design dedicated systems for recurrent and even continuous daily recording of brain activity in patients. In that respect, EEG monitoring seems more likely to truthfully reflect VS and MCS patients' complex fluctuating states than a single fMRI scan lasting a few tens of minutes. Schnakers and her colleagues showed the utility of using active EEG paradigms to probe voluntary brain responses to stimuli. They could confirm the presence of conscious processing in a locked-in syndrome patient (Schnakers, Perrin, et al., 2009), and in clinically defined MCS patients (Schnakers, Perrin, et al., 2008).

1.2.1. The 'local global' test of consciousness

We recently designed an auditory paradigm that evaluates the cerebral responses to violations of temporal regularities (Bekinschtein, Dehaene, et al., 2009). Local violations due to the unexpected occurrence of a single deviant sound among a repeated train of standard sounds led to an early response in auditory cortex, the mismatch negativity (MMN) ERP component, independent of attention and of the presence of a concurrent visual task. On the other hand, global violations, defined as the presentation of a rare and unexpected series of five sounds, led to a late and spatially distributed response that was only present when subjects were attentive and aware of the violations (P3b ERP component). We could detect the global effect in individual subjects using functional MRI and both scalp and intracerebral event-related potentials. The original publication (Bekinschtein, Dehaene, et al., 2009) reported the results from 8 non communicating patients with disorders of consciousness (4 MCS and 4 VS) and confirmed that only conscious individuals presented a global effect (3 MCS patients). In a more recent work focusing on a larger sample of clinically defined VS patients, we confirmed the absence of global effect in the vast majority of patients, and identified 2 patients showing this neural signature of consciousness (Faugeras et al., 2011). Interestingly, these 2 patients showed unequivocal clinical signs of consciousness within the 3–4 days following ERP recording, strongly suggesting they were misclassified as VS due to limitations of clinical examination. Taken together, these observations were highly suggestive that the global effect might be a signature of conscious processing, although it can be absent in conscious subjects who are not aware of the global auditory regularities.

1.3. Objectives of the present study

In the present work, we prospectively explored the first 100 consecutive recordings obtained in 65 non-communicating patients (November 2008 to February 2010) with the 'local global' paradigm while recording their EEG activity with a high-density EEG system (see Fig. 1), subsequently to a detailed neurological examination, and to a behavioral scoring of consciousness with the CRS-R. Our objectives were fourfold: (i) probe the diagnostic reliability of our test at the individual-level on a large sample of well characterized non-communicating patients with various degrees of consciousness impairments, (ii) estimate its utility in extreme situations such as "locked in syndrome" and related conditions, and (iii) explore in details the distinct ERP correlates of the violations of local and global regularities, both at the group-level and at the individual level, (iv) report the ERP correlates of task learning and stimuli expectancy. Note that the main objective of this study being the validation of the specificity of the ERP "global effect" at the individual level, we deliberately included all ERP datasets originating from various etiologies, recorded either at acute or chronic stages, and we included repeated recordings of the same patients (11 patients with 2–4 recordings) to avoid arbitrary data selection. This study does not aim at reporting specific knowledge about a given disease, of about a specific group of patients, but rather aims at testing the value of our ERP test at individual level in regards to the clinical evaluation of consciousness.

2. Materials and methods

2.1. Subjects

2.1.1. Normal controls

Experiments were approved by the Ethical Committee of the Salpêtrière hospital. The 10 normal controls (mean age = 20.3 ± 0.7; sex-ratio (M/F) = 2.3) gave written informed consent. Data from two control subjects were discarded from the analysis due to excessive movement artifacts.

2.1.2. Patients

The clinical motivation for recording patients was to better assess their level of consciousness (Bekinschtein, Dehaene, et al., 2009), and to probe potential residual unconscious processing of the auditory environment (e.g.: MMN) which predicts consciousness recovery from comatose state (Fischer, Luaute, Adeleine, & Morlet, 2004; Naccache, Puybasset, Gaillard, Serve, & Willer, 2005). Patients were recorded without sedation since at least 24 h in order to maximize their arousal and their level of cognitive performance during the auditory task. Among the 100 recordings performed on non-communicating patients, 33 were discarded from the analysis after evaluation of EEG signal quality (see below). This high rate of rejection (33%) reveals one of the intrinsic limits of this approach. Two other recordings were discarded because they were performed under sedation. The 65 valid datasets included 49 patients (32 males and 17 females, sex-ratio = 1.88), aged from 16 to 83 years (mean = 47.5 ± 17.4 years). Patients could be recorded from one to 4 times. They were affected by the following usual conditions (see Table 1 for detail): anoxia (35%), intracranial hemorrhage (28%), traumatic brain injury (18%), and other etiologies (18%). Our dataset included both early and late recordings (mean = 203 days; median = 35 days; SD = 591 days; earliest = 6 days; latest = 2555 days).

2.2. Behavioral assessment of consciousness

Clinical evaluation of consciousness was based on the French version of the CRS-R scale (Schnakers, Majerus, et al., 2008), after careful neurological examination by trained neurologists (FF, LN). This scale consists of 23 items that comprise six subscales addressing auditory, visual, motor, oromotor, communication and arousal functions. CRS-R subscales are comprised of hierarchically arranged items. The lowest item on each subscale represents reflexive activity while the highest items represent cognitively mediated behaviors. This scoring enables a distinction to be drawn between conscious (CS), minimally conscious (MCS) and vegetative (VS) states (Schnakers, Vanhaudenhuyse, et al., 2009). Clinical examination and behavioral assessment were systematically performed the same day and before EEG recording.

2.3. Auditory stimulation

We used the local-global protocol described in our previous publication (Bekinschtein, Dehaene, et al., 2009). Series of five complex 50-ms duration sounds were presented via headphones with an intensity of 70 dB and 150 ms SOA between sounds. Each sound was composed of three superimposed sinusoidal tones (either a low-pitched sound with 350 700 and 1400 Hz tones, hereafter sound A; or a high-pitched sound with 500 Hz, 1000 Hz and 2000 Hz tones, hereafter sound B). Tones were prepared with 7 ms rise and 7 ms fall times. Four different series of sounds were used, the first two using the same five sounds (AAAAA or BBBBB); and the other two with the final sound swapped (either AAAAB or BBBBA). Series of sounds were separated by a variable interval of 1350–1650 ms (50 ms steps). The blocks were designed to contain the sound series with a deviant sound in the end, either as an infrequent stimulus (block type a: 80% AAAAA/20% AAAAB; block type b: 80% BBBBB/20% BBBBA); or as a frequent stimulus (block type c: 80% AAAAB/20% AAAAA; block type d: 80% BBBBA/20% BBBBB). All block types presented a local regularity (the fifth sound could be deviant or identical to previous sounds) and a global regularity (one of the series of sounds was less frequent than the other). Each block started with 20–30 series of sounds of the frequent type in order to establish the

Table 1
Each line corresponds to one ERP recording. Age, sex, etiology, delay (days) from disease onset, lesion site, consciousness status and CRS-scoring are provided. Lines are sorted according to the consciousness status, and to CRS-R scoring.

Patient characteristics				Recordings			
Patient #	Age	Sex	Etiology	Delay	Clinical status	CRS-R	CRS-R subscores
1	62	F	ADEM	25	VS	1	0/0/0/0/0/1
2	47	F	Anoxia	54	VS	3	1/0/1/0/0/1
3	48	F	Anoxia	14	VS	3	0/0/1/1/0/1
4	51	M	TBI	11	VS	3	0/0/1/1/0/1
5	61	M	TBI	25	VS	3	0/0/0/1/0/2
6	29	F	Anoxia	85	VS	4	1/0/1/1/0/1
7	65	F	Anoxia	20	VS	4	1/0/1/1/0/1
18	**39**	**M**	**ICH**	**42**	**VS**	**4**	**1/0/1/1/0/1**
8	74	F	Anoxia	610	VS	5	1/1/1/1/0/1
9	44	M	ICH	42	VS	5	1/0/1/1/0/2
10	67	M	ICH	25	VS	5	1/1/1/1/0/1
11	41	M	ICH	350	VS	5	1/0/1/2/0/1
12	46	M	Ischemic infarction	89	VS	5	1/0/1/1/0/2
4	**51**	**M**	**TBI**	**15**	**VS**	**5**	**1/1/1/1/0/1**
13	43	F	TBI	2555	VS	5	1/0/1/1/0/2
14	22	M	Anoxia	16	VS	5	1/0/1/1/0/2
15	40	M	TBI	62	VS	6	1/1/2/1/0/1
16	76	M	Anoxia	25	VS	6	1/1/2/1/0/1
17	70	F	ICH	17	VS	6	1/1/2/1/0/1
18	39	M	ICH	37	VS	6	1/1/1/1/0/2
19	62	M	ICH	19	VS	7	1/1/2/1/0/2
20	29	M	TBI	33	VS	7	2/1/2/1/0/1
21	45	M	Anoxia	19	VS	7	2/1/1/1/0/2
22	76	F	Anoxia	46	VS	8	2/1/2/2/0/1
23	42	F	ICH	46	MCS	6	3/0/1/1/0/1
24	63	M	ICH	35	MCS	6	3/0/1/1/0/1
19	**62**	**M**	**ICH**	**154**	**MCS**	**7**	**2/0/3/1/0/1**
25	62	M	Ischemic infarction	23	MCS	7	0/3/2/1/0/1
19	**62**	**M**	**ICH**	**57**	**MCS**	**8**	**3/0/2/1/0/2**
19	**62**	**M**	**ICH**	**140**	**MCS**	**8**	**3/0/2/1/0/2**
26	55	M	Ischemic infarction	7	MCS	8	2/3/1/1/0/1
26	**55**	**M**	**Ischemic infarction**	**23**	**MCS**	**8**	**2/3/1/1/0/1**
27	21	F	TBI	29	MCS	8	1/3/1/1/0/2
28	61	M	Anoxia	6	MCS	9	3/0/2/2/1/1
29	59	M	Anoxia	17	MCS	9	2/3/2/1/0/1
29	**59**	**M**	**Anoxia**	**9**	**MCS**	**10**	**3/3/2/1/0/1**
30	39	M	TBI	26	MCS	10	3/3/1/1/0/2
16	**76**	**M**	**Anoxia**	**32**	**MCS**	**10**	**3/1/2/2/0/2**
24	**63**	**M**	**ICH**	**41**	**MCS**	**10**	**3/3/1/1/0/2**
22	**76**	**F**	**Anoxia**	**53**	**MCS**	**11**	**3/3/1/1/0/2**
31	76	M	Intracranial tumor	110	MCS	11	2/1/2/3/1/2
32	16	M	TBI	30	MCS	12	3/3/4/1/0/1
33	22	M	TBI	39	MCS	12	3/4/2/1/0/2
34	69	M	Anoxia	9	MCS	13	3/3/4/2/0/1
35	35	F	Anoxia	17	MCS	15	3/3/5/2/1/1
36	45	M	ICH	44	MCS	15	3/4/4/2/1/1
29	**59**	**M**	**Anoxia**	**23**	**MCS**	**16**	**3/4/4/2/1/1**
37	22	F	ICH	18	MCS	17	4/5/5/1/1/1
38	29	F	Anoxia	38	MCS	17	3/3/5/2/0/2
39	41	M	TBI	2555	MCS	17	4/5/1/3/1/3
40	21	F	Hypoglycemia	21	MCS	18	3/4/5/2/1/3
41	52	F	GW encephalopathy	34	MCS	19	4/5/5/2/1/2
42	30	M	Status epilepticus	2190	CS	13	3/3/1/2/2/2
43	48	M	TBI + PRN	11	CS	16	4/5/0/2/2/3
44	44	M	ICH	83	CS	16	4/5/2/2/2/1
45	83	M	PRN	11	CS	16	4/5/0/2/2/3
33	**22**	**M**	**TBI**	**49**	**CS**	**17**	**4/5/3/1/2/2**
46	49	M	Anoxia	47	CS	21	4/5/6/3/2/2
47	21	M	Anoxia	14	CS	21	4/5/6/2/2/2
36	**45**	**M**	**ICH**	**93**	**CS**	**21**	**4/5/6/2/2/2**
48	35	F	Anoxia	137	CS	22	4/5/6/3/2/2
14	**22**	**M**	**Anoxia**	**38**	**CS**	**22**	**4/5/6/3/2/2**
24	**63**	**M**	**ICH**	**57**	**CS**	**22**	**4/5/6/3/2/2**
36	**45**	**M**	**ICH**	**68**	**CS**	**22**	**4/5/6/2/2/3**
49	52	M	ICH	2555	CS	23	4/5/6/3/2/3

ADEM: acute disseminated encephalomyelitis; TBI: traumatic brain injury; ICH: intra-cerebral hemorrhage; PRN: polyradiculoneuritis; IVH: intra-ventricular hemorrhage; EDH: extra-dural hematoma; SDH: subdural hematoma; SAH: subarachnoid hemorrhage; ACoA: anterior communicant artery; ICA: internal carotid artery; MCA: middle cerebral artery. The bold value indicates additional recordings of the same patients.

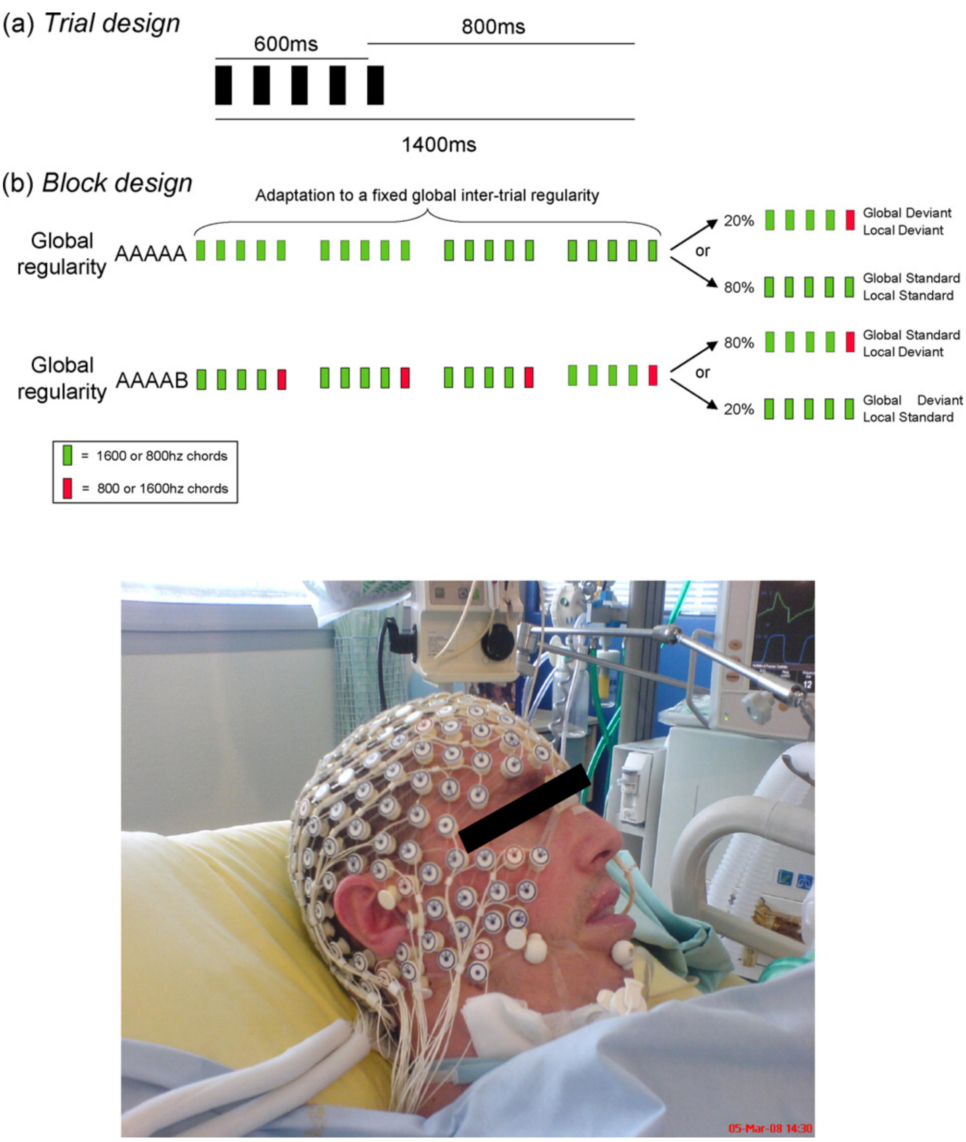

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Fig. 1. Test design and illustration of bedside recording in intensive care-unit. Top: (a) on each trial five complex sounds of 50 ms duration each were presented with a fixed stimulus onset asynchrony of 150 ms between sounds. Four different types of series of sounds were used, the first two were prepared using the same five sounds (AAAAA or BBBBB), and the second two series of sounds were either AAAAB or BBBBA. (b) Each block started with 20–30 frequent series of sounds to establish the global regularity before delivering the first infrequent global deviant stimulus. Bottom: photography of a high-density EEG recording setting of a patient in intensive care-unit (with the authorization of patient family). Installation of the net and EEG calibration requires about 15 min. Earphones are then applied, task instruction delivered, and EEG recording starts.

Adapted from Bekinschtein, Dehaene, et al. (2009) and Faugeras et al. (2011).

global regularity with 100% regular stimuli, before switching to the block with 80% frequent and 20% rare stimuli. ERPs elicited by these training trials were used to analyze the learning effect (see below). In each block the number of infrequent trials varied between 22 and 30. All stimuli were presented using Eprime v1.1 (Psychology Software Tools Inc., Pittsburgh, PA). Instructions were delivered auditorily to all patients at the beginning of each block: "*You will now listen to repetitive series of 5 sounds. At the beginning of each sequence, you will listen to the very same series which will repeat unchanged. For instance, you will be listening to repetitive series like 'bip bip bip bip bip' or 'bip bip bip bip boop'. Then, after a few tens of seconds you will listen to different series, which will differ from the previous ones. Such new series will remain rare and intermixed with frequent series identical to the initial repetitive series. Each time you will listen to such a different and rare series, we ask you to pay attention to it very carefully, and to count it in your head. Be careful, the sounds will begin in a few seconds*". All subjects heard eight blocks (3–4 min duration) in a fixed order (two runs of AAAAA, BBBBB, AAAAB, BBBBA global standards).

2.4. High-density scalp ERPs

ERPs were sampled at 250 Hz with a 256-electrode geodesic sensor net (EGI, Oregon, USA) referenced to the vertex. Trials were then segmented from −200 ms to +1300 ms relative to the onset of the first sound. We rejected voltages exceeding ±150 μV, eye-movements activity exceeding ±80 μV and eye-blinks exceeding ±150 μV. Channels with a rejection rate superior to 20% across trials were rejected. Bad channels were interpolated. Trials with more than 20 bad channels were rejected. The remaining trials were averaged in synchrony with stimulus onset, digitally transformed to an average reference, band-pass filtered (0.5–20 Hz) and corrected for baseline over the 800-ms window before fifth sound onset. All these processing stages were performed in the EGI Waveform Tools Package. Analyses of local, global and expectancy effects were done exclusively on the test trials, while the analysis of learning effect included training trials.

2.4.1. Criteria of data quality

Recording high-density scalp ERPs in ICU, or similar environments, in non-communicating patients is very challenging for technical reasons. First, the electro-magnetic environment is noisy, and patients cannot be recorded in a Faraday cage but necessarily at bedside. Second, many patients present physiological artifacts such as EMG, eye-movements and blinks, or other involuntary movements. Therefore, it is particularly important to systematically evaluate the technical quality of data before statistical analysis. Recordings including at least one block with more than 50% of rejected trials were discarded from further analyses in order to avoid possible biases across experimental conditions.

2.5. Statistics

2.5.1. Group analysis

The significance of group-level ERP effects was estimated through the 3 following approaches:

(i) Triple-threshold t-test based statistics

Matlab 7.0 (Natick, MA, USA) scripts were used to compute sample-by-sample paired t-tests across subjects. Significance threshold was defined by a triple criterion of: $p \leq 0.01$ for at least 10 consecutive samples on a minimum of 20 electrodes. Grand-average ERPs, and voltage topographical maps were performed with Cartool software programmed by Denis Brunet (http://brainmapping.unige.ch/Cartool.htm).

(ii) Regions of interests (ROI) analyses

MMN (early local effect), P3a and P3b (global effect) effects were also probed by using a ROI approach in which voltages were averaged across a group of contiguous electrodes located in the region where the corresponding ERP effect is known to peak in control subjects. In order to avoid circularity we used an independent dataset – corresponding to a recently published study using a close auditory oddball paradigm (Pegado et al., 2010) – and selected contiguous electrodes were MMN, P3a and P3b were best observed (adaptation from 128 electrodes to 256 electrodes EGI scalp nets). Using the EGI (Eugene, Oregon, USA) numbering system, these ROI corresponded to the following groups of contiguous electrodes: MMN (Fz centered: 6 7 8 14 15 16 21 22 23); P3a (Cz centered: 8 9 45 80 90 131 132 186 257); P3b (Pz centered: 100 101 110 118 119 126 128 129). Sample-by-sample t-tests were then performed with a p-value threshold at 0.01 for a minimal duration of 10 successive samples (40 ms). These ROI were also used to perform ANOVAs between groups of patients, by averaging ROI values in time within a relevant time-window (MMN: 140–180 ms; P3b: 400–600 ms).

(iii) Linear regression approach of scalp topographies

In order to take advantage of the high-spatial resolution (256 electrodes) of our recordings to detect ERP effects in patients, we complemented the electrode-by-electrode and ROI voltages analyses with a multiple-linear spatial regression approach able to exploit scalp topographies of voltages (Pegado et al., 2010). Each major ERP effect (e.g.: MMN, P3a, P3b) was defined by a 257-values vector corresponding to the averaging of voltages during the relevant time-window in controls subjects (140–180 ms for MMN; 232–368 ms for P3a; 400–600 ms for P3b). Then for each recording dataset, voltage time series (local effect and global effect) were regressed with a model including the effect of interest and a constant regressor. For each group of patients, distributions of β coefficients of interest (e.g.: MMN for local effect, P3b for global effect) were tested against the null hypothesis with a t-test ($p < 0.05$).

2.5.1.1. ERP latencies. Latencies of each effect were estimated by identifying the earliest significant time sample showing an effect (Luck, 2005), both in the triple-threshold t-test based statistics and in the ROI analyses.

2.5.2. Inter-group analyses

Concerning the inter-group analyses, we are aware of the potential bias related to the fact that our 65 ERP recordings do not correspond to 65 different patients but only to 49 patients, some of whom having been recorded several times in same or different groups. We addressed this issue by performing two analyses. First, we performed ANOVAs on a subset of 49 recordings, by keeping only one recording per patient, corresponding to the best clinical status (see SOM for additional figures on the subset of 49 subjects). Second, we also performed a general linear model analysis able to accommodate with the unbalanced design of the whole dataset, using 2 regressors (subjects group (4 levels), and subjects identity (49 levels)). This analysis took into account the presence of some repeated recordings of the same subjects. Both analyses are complementary and allow avoiding arbitrary data selection.

2.5.3. Individual subject analysis

For individual subject statistics, unpaired t-tests across trials were calculated for each time sample. Significance threshold was defined by a triple criterion: $p \leq 0.01$ on a minimum of 5 consecutive samples, on a minimum of 10 electrodes. In order to further assess the power of observed effects, we categorized the significance of the local and global effects for each time-sample using a 5-level p-value scale: <0.01, <0.005, <0.001, <0.0005, <0.0001. A last correction was then used on each recording in order to increase the specificity of our analyses. Given that local effects begin in controls around 100 ms after the onset of the fifth tone, all p-values of interest (100–736 ms after fifth tone onset) superior to the lowest p-values observed in this recording within the baseline time-window (−800 to 0 ms) were discarded. Finally when p-values of interest were equal to this minimal p-value, the effect was considered significant only if its duration exceeded the longest duration observed at this p-value level within the baseline time-window. A similar correction was applied for the global effect, with a different time-window of interest (200–736 ms). Learning effects time windows were respectively 108–244 ms after first sound onset (early effect), and 200–736 ms after fifth sound onset (late effect).

2.5.4. Permutation statistics

We further checked the statistical significance of our t-test based triple threshold statistics through Monte-Carlo permutations, both for group-level and individual-level analyses. This procedure is particularly relevant to estimate the statistical significance of effects observed with a signal of unknown distribution (Manly, 1997). For group-level statistics, we calculated the shorter duration of observed effects satisfying our paired t-test thresholds, and then computed random permutations in two surrogate groups with the same dataset, and counted the number of surrogate effects satisfying our criterion (a minimum of 10 consecutive samples with paired t-test $p \leq 0.01$ on a minimum of 20 electrodes) anywhere in the relevant ERP time window (100–735 ms). The number of permutations was set to 2000 for most analyses: note that only 255 permutations were computed for the analyses performed on the group 8 controls, in which only $2^8 = 256$ distinct permutations exist. We then computed the observed probability of this criterion (number of surrogate effects per 2000), and used this proportion as an estimate of the first-order α risk. For individual analyses, the same procedure was used with unpaired t-tests, with 2000 permutations. For each analysis, both at the group-level and at the individual-level, a criterion of $p \leq 0.05$ on permutation tests was required to consider the effect as significant (see Naccache, Gaillard, et al., 2005; Naccache, Puybasset, et al., 2005 for a recent use of this methodology in an intra-cranial ERP study).

3. Results

3.1. Behavioral assessment of consciousness

Among the 100 recordings, 65 were considered as valid on the basis of our procedure of EEG quality evaluation (see Section 2). These 65 correct recordings corresponded to 49 patients, some of whom were recorded several times (from 1 to 4). This heterogeneous collection of recordings included various levels of clinically assessed conscious states ranging from VS, MCS to overtly conscious, and conscious but paralyzed patients. More precisely, these 65 recordings corresponded to: 24 recordings within VS (37% of recordings), 28 recordings within MCS (43% of recordings), and 13 recordings within CS (20% of recordings). Detailed descriptions of clinical characteristics are reported in Table 1. Note that 4 patients presented with severe central or peripheral motor impairments which limited the sensitivity of behavioral evaluations: patient #37 suffered from a brainstem cystic tumor complicated by a brainstem hemorrhage (MCS, CRS-R = 17), and patient #44 was in a locked-in syndrome caused by a pontic compression secondary to a right cerebellar hemorrhage associated to a right vertebral dissection (CS, CRS-R = 16). Patients #43 and #45 were affected by a severe polyradiculoneuropathy (Guillain–Barré polyradiculoneuritis). However, careful examination was sufficient to reveal behavioral signs of consciousness in these two patients (CRS-R = 16 for the two patients).

3.2. Event-related potentials

We analyzed ERP data by focusing on 4 electrophysiological effects. We first describe the two effects we previously reported (Bekinschtein, Dehaene, et al., 2009; Faugeras et al., 2011): the (1) “local” and (2) “global” effects. We also report here two new ERP effects: (3) the early cortical processing of sounds, and (4) a learning effect.

For each of these 4 ERP effects, results are reported both at the group level and at the individual level.

3.2.1. ‘Local effect’: responses to violations of short time-scale regularities

3.2.1.1. Group analyses. We first examined brain responses to violations of local (intra-trial) regularity at the group level, by comparing local-deviant (LD) trials ERPs with local-standard (LS) trials ERPs in each of the 4 groups (see Fig. 2 bottom panel, and SOM figure for detailed scalp topographies of local and global effects).

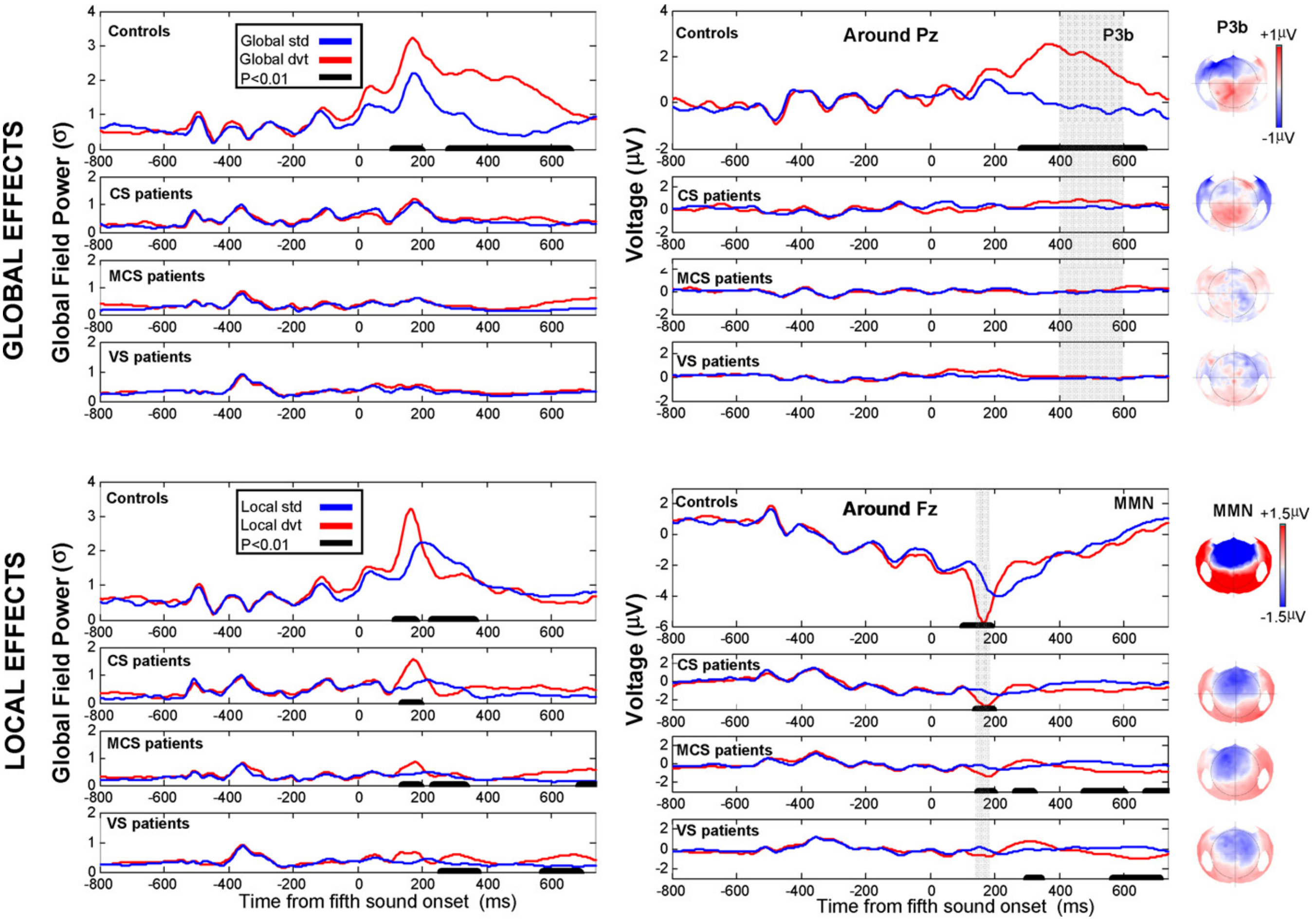

Fig. 2. Local and global effects at the group level. Left: dynamics of global field power (GFP) for the global regularity conditions (top panel), and for the local regularity conditions (bottom panel). Global and local standard (blue curves) and deviant (red curves) GFPs are plotted, and each significant difference between standard and deviant voltages is indicated by a black marker on the X-axis (see Section 2 for details). Middle: dynamics of ERPs on two regions of interests. Global effect is plotted around Pz (top panel), where a significant P3b component is observed exclusively for the conscious controls group. Local effect is plotted around Fz (bottom panel), where a large MMN is present for conscious controls, and decreases progressively in relation to the severity of consciousness impairment. Right: ERP scalp topographies of the P3b global effect (top) averaged across the gray shadowed time-window (400–600 ms). Bottom topographies indicate the MMN local effect across the corresponding time-window (140–180 ms).

In the controls group, we replicated our previous findings (Bekinschtein, Dehaene, et al., 2009) by observing 4 main results: (1) the absence of local effect up to 100 ms after fifth tone onset, (2) a first effect ranging from 124 to 184 ms with a voltage topography corresponding to a typical MMN, (3) a vertex-centered positivity immediately following this MMN ranging from 232 to 368 ms, and (4) the absence of any later effects. These two effects were found significant both with the triple-threshold *t*-test based statistics and with the ROI analyses (see Section 2).

In the conscious patients group, the MMN was present and significant (see Fig. 2). A linear regression analysis confirmed the scalp topography of this MMN effect (see Section 2; mean $\beta = 0.24$; $p = 0.001$; see Fig. 2, lower right column). The vertex-centered positivity was visible on scalp topographies and confirmed with the linear regression analysis, but did not reach significance in our 2 other statistical approaches (triple-threshold *t*-test based statistics, and ROI analyses). No late local effects were observed in this group.

In the MCS patients group, both the MMN, and the following positivity (236–340 ms) were found significant with our 3 statistical approaches (for the linear regression analysis of MMN: mean $\beta = 0.17$; $p = 0.0015$), and a late local effect was observed as an anterior centered negativity occurring between 688 and 736 ms.

In the VS patients group the MMN was not significant according to the triple-threshold statistics and to the ROI analysis, but was observed with the linear regression analysis, $\beta = 0.15$; and $p = 0.005$). The vertex-centered positivity was significant with our 3 measures and spanned from 260 to 372 ms. Finally, the late anterior negativity observed in the MCS group was present in VS patients group, from 576 to 692 ms.

When comparing these four groups, MMN amplitude and significance seemed to be strongly related to the level of consciousness (see Fig. 2, right bottom panel): the better the patients were in terms of consciousness status, the larger and the stronger their MMNs were. We first tested the amplitude effect by running a one-way ANOVA, restricted to controls and to the subset of 49 patients with only one recording per patient (see Section 2), with the group (4) factor on the voltage averaged in space across a ROI centered around Fz and in time across a [140–180 ms] temporal window. This analysis revealed a main effect of the group factor ($F(3,54) = 4.8$; $p = 0.005$), and a linear contrast confirmed that MMN amplitudes increased with higher levels of consciousness ($F(1,54) = 13.9$; $p = 0.0005$ for the linear contrast testing the following order in MMN amplitude: Controls > Conscious patients > MCS patients > VS patients). We also tested the same amplitude effect on the whole dataset of recordings by running a general linear model analysis with two regressors, including group factor and subject identity factor (see Section 2). This analysis replicated the modulation of MMN amplitude across groups ($F(3,68) = 3.2$; $p = 0.03$).

We also estimated and compared MMN latencies across groups. When first analyzing the triple-threshold data, MMN latency was measured at 124 ms after fifth tone onset in controls, and it was delayed to 140 ms both in conscious and in MCS patients. Given that MMN was not significant at the group-level for the VS patients in our triple-threshold *t*-test based statistics, we also estimated latencies through the ROI analysis. In this more sensitive analysis, MMN latencies were estimated at 104 ms, 144 ms, 152 ms and 152 ms respectively for controls, CS patients, MCS patients and VS patients. Note however that a one-way ANOVA performed on individual MMN latencies did not reveal any significant differences across the 4 groups ($p > 0.5$ both for the main effect, and for a linear contrast respecting clinical progression).

3.2.1.2. Individual analyses. MMN was observed in 7/8 controls (87.5%), in 8/13 recordings of CS patients (61.6%), in 9/28 recordings of MCS patients (32.1%), and in 6/24 recordings of VS patients (25%) (see Fig. 3). MMN presence was therefore affected by consciousness status (logistic regression test with the 4 groups declared as a predictor of MMN presence: $p = 0.0005$). This effect was still present but more modest when restricting the analysis to the 3 patients groups ($p = 0.04$). A trend of a relation was observed between the CRS score and the presence of a MMN (mean CRS for MMN+ = 12.3 and mean CRS for MMN− = 9.5; the Student *t*-test unilateral *p* value = 0.04). While MMN presence was not different between MCS and VS patients groups ($p = 0.6$ in a χ^2 test), MMN was statistically more significant in MCS patients than in VS patients (see Fig. 3). Indeed, an ANOVA with two orthogonal factors: group (4) X Local_regularity (2) performed on the voltage averaged in space across a ROI centered around Fz and in time across a [140–180 ms] temporal window revealed that MMN amplitude increased with higher levels of consciousness ($F(1,138) = 4.9$; $p = 0.03$ for the linear contrast testing the following order in MMN amplitude: Controls > Conscious patients > MCS patients > VS patients).

3.2.2. The ‘global effect’: responses to violations of long time-scale regularities

3.2.2.1. Group analyses. In the controls, a large global effect was visible on the global field power (GFP) plots, on averaged ERP curves and on scalp topographies (see SOM figure), and was confirmed with our statistical criterion (see Fig. 2, top panels). This global effect spanned from 284 to 660 ms after the onset of fifth tone, in close agreement with our previous findings. This effect presented a clear P3 topography, beginning with a vertex-centered positivity (P3a) and followed by a more posterior Pz-centered positivity (P3b). Note that before this large and late P3 complex, an earlier and shorter global effect was observed within the MMN window of the local effect, with a similar topography. On the basis of our previous findings which related the large and sustained P3b response to consciousness of the global rule, we focused on this ERP component, and performed a ROI analysis. Voltages were averaged for each control subject across a set of electrodes surrounding Pz (see upper left panel on Fig. 2), and a sample-by-sample *t*-test was performed (see Section 2). P3b latency in controls was estimated at 448 ms after the fifth sound with the ROI analysis. Note that the triple-threshold statistics revealed an earlier effect (284 ms) corresponding to a P3a effect as mentioned above. A dedicated Cz-centered similar ROI analysis estimated P3a latency at 320 ms in controls.

In conscious patients, neither the triple-threshold statistics nor the ROI analysis could identify a P3b global effect. Nor could the earlier global effect be observed in this group. We then ran the regression analysis to capture a significant P3b effect in this group on the basis of scalp topography information (see above). While visual inspection revealed a scalp topography reminiscent of the P3b on grand-average data (see Fig. 2, lower right topographies), the statistical distribution of individual β values of the P3b regressor did not differ from 0 ($p > 0.4$). For the two other groups (MCS and VS patients) none of these 3 analyses could isolate a significant global effect at the group level.

We could then test for the inter-group differences by running an ANOVA – restricted to controls and to the subset of 49 patients – with a group (4) factor, on the global effect voltages averaged across the Pz ROI during the P3b time-window. This analysis confirmed the existence of a strong modulation of P3b with conscious status ($F(3,54) = 14.7$, $p < 10^{-5}$). This modulation followed the order of consciousness: Conscious controls > Conscious patients > MCS patients > VS patients (linear contrast: $F(1,54) = 40.9$, $p < 10^{-5}$). A general linear model analysis performed on the whole dataset of recordings replicated this effect ($F(3,68) = 6.5$; $p = 0.0006$).

3.2.2.2. Individual analyses. We observed a significant global effect in each of the 8 controls (100%) within the 300–700 ms temporal window after 5th sound onset (see Fig. 4), replicating our previous findings (see our control group #1 in Bekinschtein, Dehaene, et al., 2009). In the patients groups, the proportions of individuals showing a significant global effect fell respectively to 7/13 (53.8%) recordings of CS patients, 4/28 (14.3%) recordings of MCS patients, and 2/24 (8%) recordings of VS patients. These differences were highly significant across groups – as in above the group level analysis ($p < 10^{-7}$ in a logistic regression test). An additional analysis confirmed the strong relation prevailing between the CRS score and the presence of a global effect (mean CRS for GE+ = 14.7, and mean CRS for GE− = 9.5; $p = 0.002$ in a two-sample *t*-test).

Of particular interest are the VS patients results, we previously reported in a dedicated publication (Faugeras et al., 2011). First, the vast majority of VS patients did not show global effect (2/22). Most notably, only two VS patients showed a global effect, and for both of them the immediate clinical evolution was marked by the recovery of behavioral signs of consciousness within 3 and 4 days after EEG recordings, respectively (see patient #1 and patient #4’s second recording in Table 1). These two cases are reminiscent of recent reports of the few patients clinically assessed as VS – on the basis of a detailed clinical examination and CRS scoring – who showed evidence of consciousness in active fMRI paradigms (Monti et al., 2010; Owen et al., 2006). Similarly, our two observations may correspond to such a situation in which neurophysiological probing of consciousness may go beyond clinical evaluation. In favor of such an interpretation note that by contrast, in the 20 remaining VS patients without an ERP global effect, early recovery of consciousness was observed in only 2 cases within the first week following ERP recording ($\chi^2 = 9.90$, $p = 0.002$; Exact Fischer test: $p = 0.026$; see Faugeras et al., 2011 for a detailed report of the VS patients group).

Thus, the global effect proved to be an almost 100% specific test of consciousness. Even if the 2 VS patients showing a global effect and who recovered behavioral signs of consciousness are classified as “false positive” subjects we obtain the following values: specificity (correct rejections/(false positives + correct rejections)) = 91.7%; positive predictive value (hits/(hits + false positives)) = 84.6%; sensitivity (hits/(hits + false negatives)) = 26.8%; and negative predictive value (correct rejections/(correct rejections + false negatives)) = 42.3%. Alternatively, if we classify these 2 VS patients as conscious subjects, then we obtain a specificity and a positive predictive value of 100%.

3.2.3. Early cortical processing of sounds

We then explored ERPs prior to the processing of local and global regularities. Given the strong differences in both local and global effects in relation to conscious status of patients, we wondered if even earlier differences could be observed.

3.2.3.1. Group analyses. We inspected responses to auditory sounds across a region of interest defined by the 23 electrodes

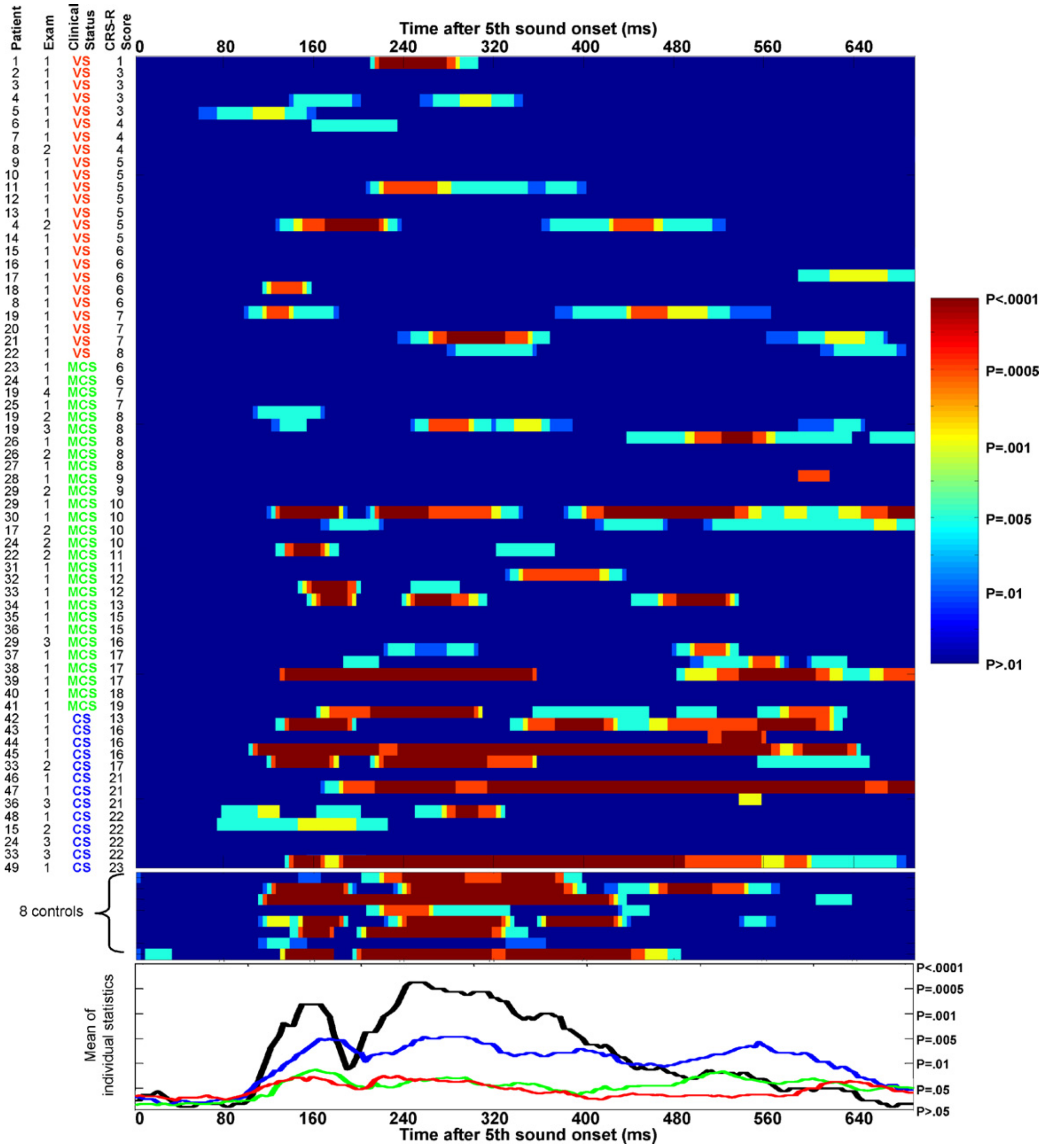

Fig. 3. Local effect at the individual level. Each horizontal line corresponds to one ERP recording. On the left, clinical characteristics are indicated, including patient conscious state, and CRS-R scoring. Recordings are sorted from VS patients to conscious patients, and in each category from low to high CRS-R scores. For each recording, the presence of any significant ERP local effect – tested with the triple-threshold *t*-test based statistics confirmed with Monte-Carlo permutation analyses detailed in Section 2 – is indicated by a color-code. A similar plotting is showed for each of the 8 controls where a MMN could be detected for each subject. The graph located at the bottom represents the mean of individual statistics for each group.

surrounding the vertex electrode (Cz), where early cortical responses to sounds are best observed (see Fig. 5). For each recording of the subset of 49 patients, we averaged ERPs around Cz across all global standard trials, applied a 200 ms baseline correction, and submitted these values to a sample-by-sample one-way ANOVA with the group (4) factor. A cortical response to each of the first four sounds was visible in the 4 groups (see Fig. 5, top panel). Interestingly, early cortical processing of the sounds was not affected by clinical status up to ∼250 ms after the onset of the first of the five sounds defining each trial. This finding is highly consistent with the large group of studies reporting spared early non-conscious processing in comatose or VS patients, and consequently confirms the need to disentangle between neural markers of conscious versus non-conscious processing. From ∼250 ms up to ∼1100 ms after the onset of the first sound, significant differences were observed across groups (p values < 0.05; a very same pattern of significance was observed when analyzing the whole recordings dataset using a general linear model analysis taking into account subject identity). These inter-group differences corresponded mostly to a difference in the strength of a negative drift ending during the processing of the fifth sound which is the event defining the nature of the trial (local and global regularities). While this negative drift was visually obvious for controls, and to a lesser degree for conscious patients, it seemed less present for the two other groups of patients. For each group, and also for each individual recording, we computed the linear regression of these averaged ERPs within the [0–600 ms] time-window running from the onset of the first sound up to the onset of the fifth sound. This analysis confirmed the existence of a significant negative slope for controls ($R^2 = 0.64$; all individual slopes were negative; t-test p value < 10^{-4} when comparing slopes

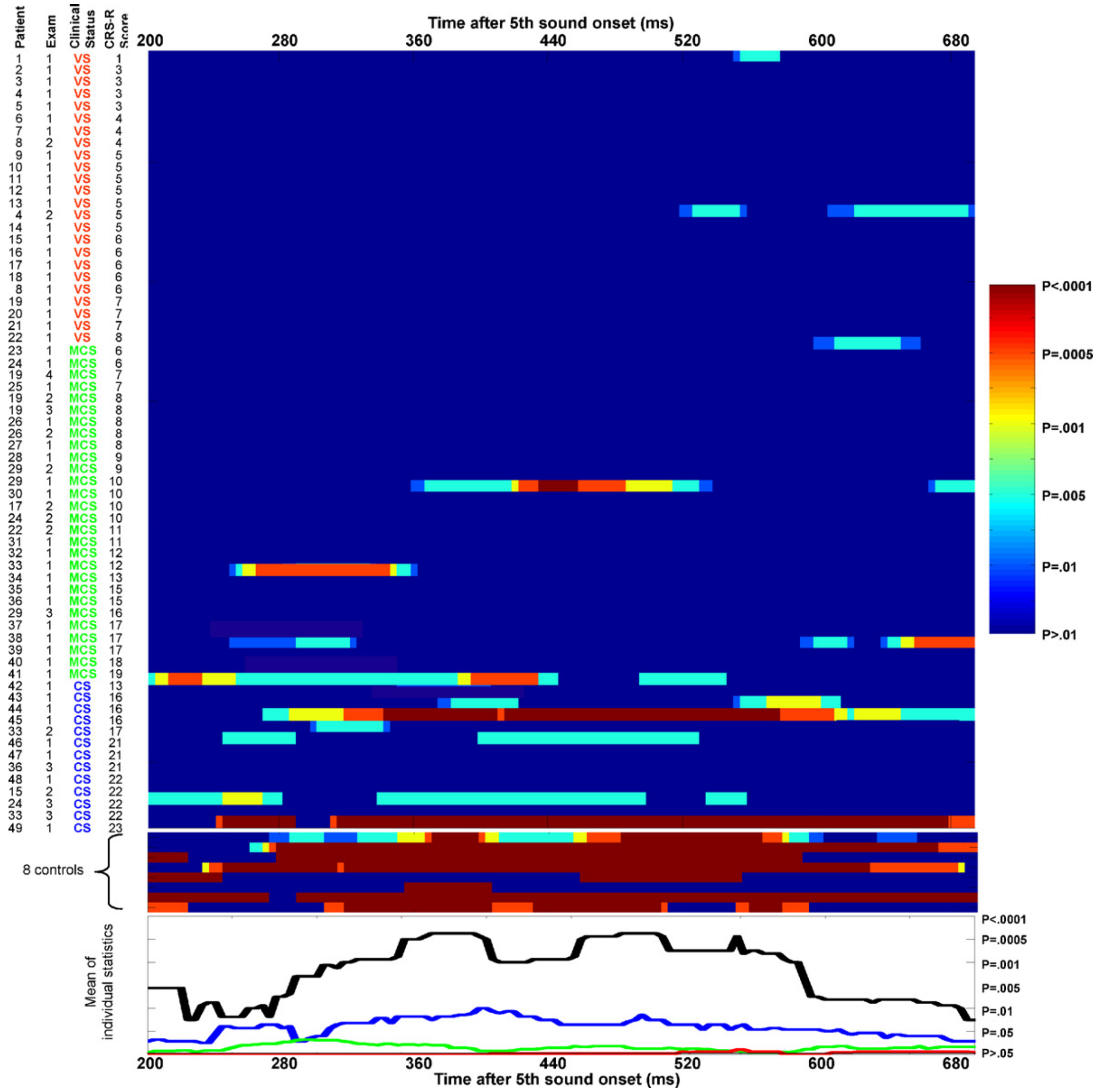

Fig. 4. Global effect at the individual level. This figure was created using the very same design as in Fig. 3. Note that a global effect could be detected in each of the 8 control subjects. In patients, global effects were observed only in conscious or MCS patients. The only 2 VS patients with a global effect showed clear behavioral signs of consciousness within the 3–4 days after recording, suggesting that they were conscious during ERP recording (see text).

distribution to a zero-centered distribution) and for conscious patients ($R^2 = 0.45$, all individual slopes were negative; *t*-test *p* value < 10^{-4}), while this effect was absent for the two other groups ($R^2 = 0.10$, $p = 0.1$ for MCS patients; and $R^2 = 0.26$, $p = 0.06$ for VS patients). An ANOVA performed on controls data and on the subset of 49 patients confirmed the significance of slope differences across the 4 groups ($F(3,54) = 5.0$, $p = 0.004$). The general linear model analysis ran on the whole dataset showed a similar, but weaker, effect ($F(3,68) = 2.7$, $p = 0.05$).

This slow ERP effect is suggestive of the classical 'Contingent Negative Variation' (see Walter, Cooper, Aldridge, McCallum, & Winter, 1964 and discussion section) on the basis of 3 arguments: (1) it is an early effect beginning with the early perceptual processing of the first sound – which is probably reflecting an expectancy of the delivery of the fifth sound, the sound that conveys the critical information about local and global regularities of the trial – and ending when this last sound is processed; (2) it presents an anterior negativity scalp topography reminiscent of the CNV; and (3) it is observed exclusively in the groups of clearly conscious subjects (controls and CS groups), more prone to deploy expectative cognitive processes than the two other groups. Therefore, we will now refer to this early negative drift effect as a CNV.

3.2.3.2. Individual analyses. At the individual level, a linear regression was calculated for each individual trial on the vertex centered ROI during the [0–600 ms] time-window of interest. Then the distribution of these individual trials slopes was compared to zero with a one-sample Student *t*-test. A significant CNV was observed in each of the 8 controls (100%), in 8/13 (61%) recordings of conscious patients, in 12/28 (43%) recordings of MCS patients, and in 9/24 (37%) recordings of VS patients (see Fig. 5, middle panel). In patients, CNV was not more present in MCS or conscious state recordings than in VS recordings ($p = 0.4$ in a χ^2 test). Most of recordings showing a global effect had a CNV (61%). However, the presence of a CNV was not strongly associated with global effect ($p = 0.2$ in a χ^2 test). Recordings with a CNV were slightly more prone to present a MMN ($p = 0.06$ in a χ^2 test). In order to determine the impact of CNV presence on local and global effects at the group level, we then categorized each recording either as CNV+ or as CNV−, and computed local and global effects in these two

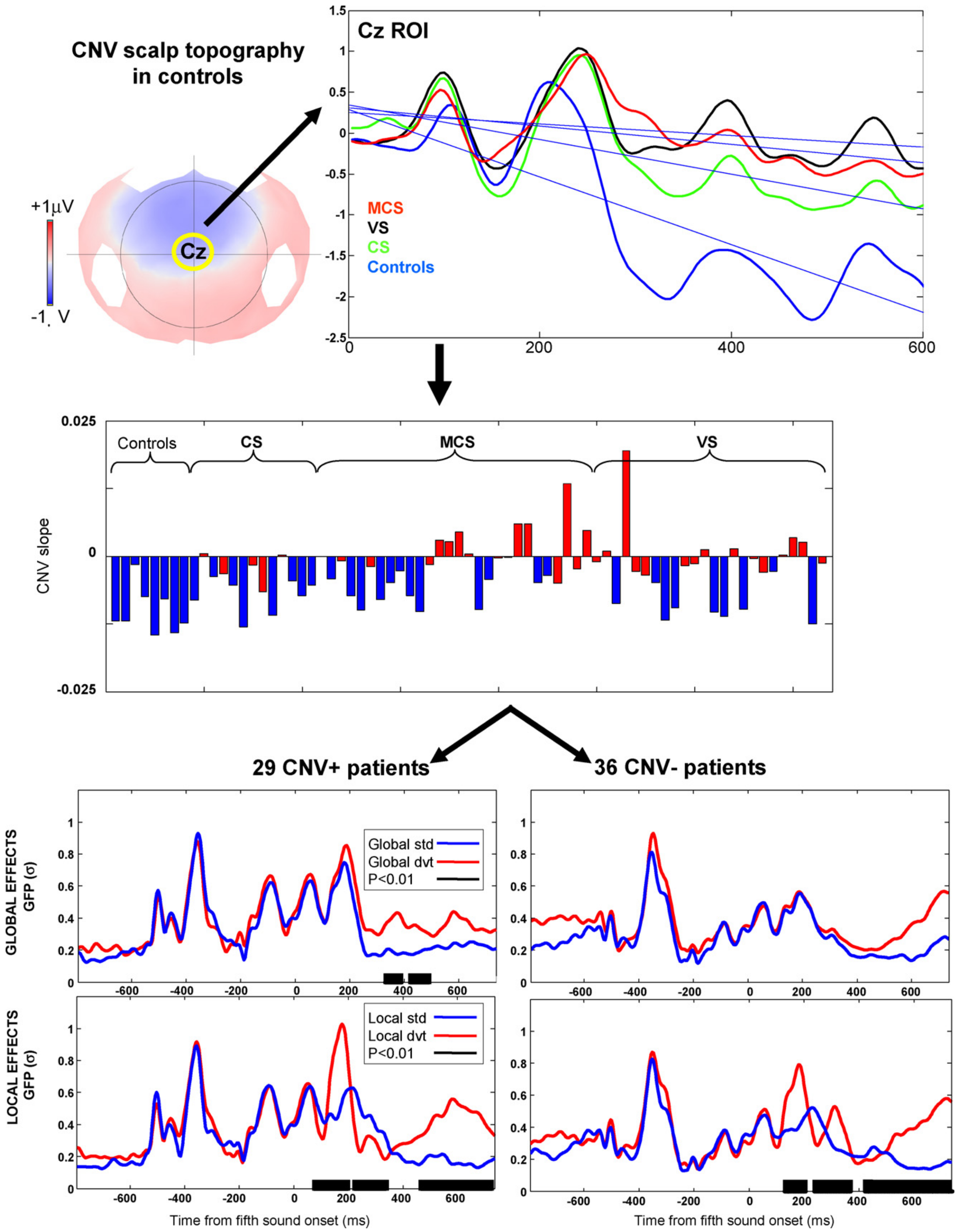

Fig. 5. CNV predicts global effect in patients. Top: in controls, scalp topography of voltage averaged from 0 to 600 ms after the onset of the first sound reveals an anterior negativity maximum around Cz and corresponding to an expectation CNV (left). Voltage averaged around Cz is plotted for each group of subjects, and linear regressions show a progressive decrease of CNV slope from controls to VS patients (right). Middle: CNV slope is shown for each individual recording. Each recording was categorized as CNV+ (blue bars) or CNV− (red bars) after comparing individual distributions of single-trials slopes with zero. Bottom: global (top) and local (bottom) dynamics of GFP are plotted separately for the CNV+ (left) and CNV− (right) patients groups. Global and local standard (blue curves) and deviant (red curves) GFPs are plotted, and each significant difference between standard and deviant voltages is indicated by a black marker on the *X*-axis. A global effect is observed in the CNV+ group.

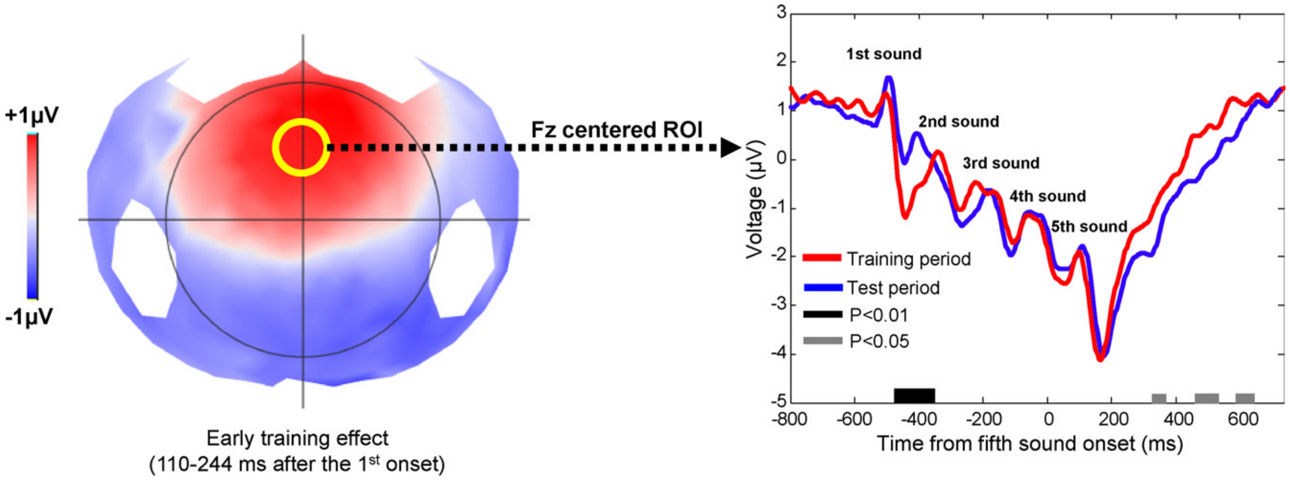

Fig. 6. Learning effect in controls. Left: scalp topography of test minus training ERPs of global standards trials averaged across 110–244 ms after first sound onset, in controls. Right: dynamics of Fz centered ERPs of training (red) and test (blue) averaged ERPs reveal two effects, one occurring before the fifth sound, and a second one occurring later and statistically weaker.

groups. If the CNV does index cognitive expectations of stimuli regularities, one should predict that CNV presence should increase the likelihood of observing other markers of the processing of auditory regularities. In particular, under such a hypothesis both global effect and late local effect should be more important in CNV+ recordings than in CNV− recordings.

Local effects did not differ between CNV+ and CNV− groups (see Fig. 5, bottom panel). In particular, MMN, P3a and late local effect were present and comparable (all p values > 0.5 on t-tests performed on Fz ROI during MMN time window, on Cz ROI during the positivity immediately following the MMN, and during the late local effect). In sharp contrast, global effect was observed only in the CNV+ group, while it was absent in the CNV− group.

3.2.4. *Learning effect*

Finally, we looked for learning effect by taking advantage of recording the EEG signal both during the training and testing periods. Each block began with the delivery of verbal instructions followed by 20–30 series of frequent type in order to establish the global regularity with 100% regular stimuli. Then, the testing period followed without interruption, with 80% series of the frequent type ("global standards"), and 20% of the rare type ("global deviants"). While all previous analyses focused on the testing period, we compared here the processing of the very same physical stimuli ("global standards"), according to the period during which they were processed (learning versus testing periods).

3.2.4.1. Group analyses. In controls, this comparison revealed two learning effects visible on the anterior, Fz-centered, region: first, an anterior positivity (testing trials minus training trials) occurring around 108–244 ms after first sound onset, followed by a delay effect presenting like an anterior negativity occurring around 312–620 ms after fifth sound onset (see Fig. 6). This second effect was statistically weaker.

In the conscious patients group only the second effect was observed, while none of these 2 effects was present in MCS and VS patients groups.

The first effect was also observed when contrasting global standard trials from the learning period with global deviant trials from the testing phase. Indeed, the time-window of this effect is located before the onset of the fifth sound. Obviously, such an analysis is not relevant for the late effect which overlapped with the global effect.

3.2.4.2. Individual analyses. In controls, 4/8 showed the first effect, while 2/8 showed the late effect. Taken together 5/8 conscious controls showed a learning effect. In conscious patients, 2/13 recordings showed the early effect, and 5/13 showed a significant late effect. Among MCS patients, 5/28 recordings showed the early effect, and 2/28 the late effect. Finally within VS patients, only one recording showed the early effect, and another patient had a late effect. Interestingly, the clinically 'VS' patient with the early learning effect was one of the two who presented a global effect and who were probably misclassified and conscious during the recording (see above and discussion, and Faugeras et al., 2011).

4. Discussion

In this work we prospectively recorded high-density scalp ERP in patients suffering from various disorders of consciousness, while they were instructed to perform an active version of the 'local global test'. This test was recently designed to diagnose consciousness without relying on behavioral responses. Among these 100 recordings, 65 satisfied criteria of data quality, due to the large amount of motor and environment EEG artifacts. Both the clinical condition of patients who were recorded in the absence of any sedative drugs – enabling therefore motion artifacts – and the noisy electrical environment inherent to intensive care units most probably contribute to explain this high-rate of data rejection. The acceptable recordings correspond to 49 patients, some of whom were recorded several times.

4.1. *Strength of the global effect for probing consciousness: a positive predictive value close to 100%*

The presence of an ERP global effect proved to be an extremely specific measure of consciousness: among the 13 recordings showing a global effect, 11 corresponded to conscious patients (MCS or conscious states) and only 2 were observed in clinically diagnosed VS patients. Crucially, in these 2 patients recorded during the acute phase of their consciousness disorder (see Table 1, patient #1 and second recording of patient #4 on line 14), univocal behavioral signs of consciousness were present respectively 3 and 4 days after recording (see Faugeras et al., 2011). In other terms, these two observations most probably illustrate situations in which neurophysiological data can go beyond the sensitivity of behavioral measures to probe consciousness, as it was recently reported with an active mental imagery task in fMRI (Monti et al., 2010; Owen et al., 2006). In addition to these two extreme cases, we could also demonstrate the usefulness of this test in 2 conscious patients affected with a severe acute polyradiculoneuropathy (Guillain–Barré syndrome) who showed a clear global effect confirming the clinical diagnosis (see Table 1, patient #45 and patient #43) of consciousness. In these two patients, behavioral signs of consciousness were subtle and called for careful inspection. For instance, in one of these patients, the only voluntary movements were limited to discrete lateral flexions of the neck initially discovered by an expert ICU neurologist (FB). As a provisional conclusion the 'local global' test demonstrated its clinical robustness and its positive predictive value to probe consciousness in non-communicating patients. Of major interest, this test seems powerful enough to provide reliable measures at the individual level.

Our finding that the global effect is observed exclusively in conscious patients is equally important for theories of consciousness. The 'local global' test is based on the global workspace theory of conscious processing which postulates that consciousness is required to actively maintain perceptual information over time in working memory, and to engage strategical processes necessary to detect and count the global deviance occurrences (Bekinschtein, Dehaene, et al., 2009; Dehaene & Naccache, 2001). We previously showed that in conscious controls the global effect is abolished when attention is captured by a concurrent visual task. In this experimental condition (see Experiment 3 of Bekinschtein, Dehaene, et al., 2009), subjects could not consciously report the presence of a global regularity after the recording. However, one could have imagined that the limiting factor in this case was not consciousness per se, but rather the availability of cognitive resources engaged by top-down conscious processing in another task. In other terms, an important complementary condition is to demonstrate that the global effect does not occur in non conscious patients in whom residual cognitive abilities are not engaged in an active distracting task. The present study strengthens the causal relation prevailing between consciousness and the cognitive processes at work in the 'local global' paradigm. Our work therefore confirms that active maintenance of perceptual information during an arbitrary task requires consciousness. Additionally our results also reinforce the set of recent studies proposing that late P3b-like ERP scalp topographies may constitute a specific neural signature of conscious access (Gaillard et al., 2009; Sergent, Baillet, & Dehaene, 2005).

4.2. Limits of the global effect: a low negative predictive value

In spite of its high specificity and positive predictive value, the global effect presents a much less satisfactory sensitivity (~27%) and negative predictive value (~42%), indicating that many patients easily classified as conscious by clinical criteria do not show a significant global effect in ERPs. Several factors may concur to explain this lack of sensitivity. First, auditory processing prior to cortical stages has to be preserved to allow the presence of a global effect (obviously, a deaf conscious patient would not show any global effect). Careful clinical examination (sound localization responses, auditory startle response) and inspection of preserved P1/N1 to auditory stimuli are strong arguments to discard such an explanation. Note that in the presence of any doubt of deafness, brainstem auditory evoked potentials (BAEP) are to be recorded. Second, the presence of a global effect not only requires the patient to be awake and conscious during the recording, but also that he/she would understand the instructions, be able to keep perceptual representations in working memory, memorize task instructions and continuously perform the task. In other terms, a conscious patient affected with cognitive impairments in any of the listed processes may perfectly well miss the task. Our group analyses suggest that in such cases, a conscious patient unable to perform the global task may well process consciously the local regularity, as shown by the presence of late local effects in the MCS and VS groups, while both conscious controls and conscious patients presenting a global effect did not show any late local effect. On the other side, the presence of an ERP global effect may well be considered as the sign of a rich conscious cognition, and could prove to be a useful index of cognitive outcome. Future outcome studies should elucidate this point. The limits exposed here are inherent to many active cognitive paradigms (Naccache, 2006; Owen et al., 2006). In the same vein, fluctuations of attention or arousal may impair task performance. Some of these limitations could be overcome by sorting individual trials on the basis of additional EEG measures more related to arousal or attention (e.g.: proportion of slow waves, measures of coherence and/or EEG complexity indexes such as EEG entropy or EEG dimensional activation, Velly et al., 2007). The current emergence of brain–computer interfaces allowing such analyses to be performed in real-time on a single-trial basis may well significantly increase the sensitivity of our test (Delorme & Makeig, 2004; Thulasidas, Guan, & Wu, 2006). Note that in spite of its low sensitivity, this test is of medical interest because clinical consensus on patients' consciousness status is often erroneous, as recently reported by Schnakers, Perrin, et al. (2009) and Schnakers, Vanhaudenhuyse, et al. (2009): "*Of the 44 patients diagnosed with VS based on the clinical consensus of the medical team, 18 (41%) were found to be in MCS following standardized assessment with the CRS-R.*" In other terms, when focusing on the VS and MCS patients who are difficult to classify reliably on standard clinical measures – without fine behavioral measures such as the CRS-R – it is not absolutely useless to find 6 positive recordings out of 52. ERPs added some confidence for the MCS patients, and corrected the functional diagnosis in two clinically VS patients.

4.3. ERP responses to violations of local regularities

Violations of local regularities elicited three successive ERP effects, the occurrence of which differed across groups. First, a classical MMN response was observed within 140–180 ms after fifth tone onset. Interestingly, MMN was affected by clinical status: it was larger, better delineated (scalp topography), and more significant in the groups of conscious controls and conscious patients than in MCS and VS patients groups. This result is in agreement with a recent study reporting a progressive increase of MMN quality during the VS to MCS transition in a few individual patients (Wijnen, van Boxtel, Eilander, & de Gelder, 2007). Given that early MMN (90–160 ms) is a pre-attentional automatic ERP component impermeable to conscious top-down processes (Naatanen, Tervaniemi, Sussman, Paavilainen, & Winkler, 2001; Pegado et al., 2010; Tiitinen, May, Reinikainen, & Naatanen, 1994), and given that it has been reliably observed in comatose and VS patients (Bekinschtein, Dehaene, et al., 2009; Fischer, Luaute, et al., 2004; Fischer, Morlet, et al., 1999; Kane, Curry, Butler, & Cummins, 1993; Naccache, Puybasset, et al., 2005), the finding that even early MMN is impaired in MCS and VS patients indicate that these patients are not characterized by 'pure' impairments of consciousness, but that they most probably combine arousal and perceptual deficits to disorders of consciousness. This highly plausible interpretation is supported by recent works questioning the definition of VS as a pure dissociation between a preserved arousal function, and an impaired consciousness. For instance, Bekinschtein, Golombek, et al. (2009) showed that while VS patient are able to keep their eyes open spontaneously, they do not show normal circadian rhythms of body temperature or other physiological markers. Therefore, the combination of neurophysiological markers exploring both conscious processing (e.g.: P3b global effect response) and unconscious perceptual abilities (e.g.: early local effects) may help to better estimate the range of preserved cognitive faculties. In this perspective, the design and use of multifaceted ERP batteries exploring distinct cognitive processes in the same patient would be promising. For instance, the combination of paradigms probing verbal semantic processing (N400 word priming experiments, Rama et al., 2010), verbal syntactic decoding (P600 sentence paradigms, Kotchoubey, 2005), and emotional processing of meaningful stimuli (e.g.: processing of known voices or own name, Holeckova, Fischer, Giard, Delpuech, & Morlet, 2006), in addition to MMN and markers of conscious access may prove useful both for diagnostic and cognitive prognosis issues. The present study reinforces the relevance of this approach.

Second, immediately following the MMN response we observed an anterior positivity response which may well correspond to a P3a response indexing a central stage of processing of local deviance. Indeed, the finding that this component was less significant both in the groups of control subjects and in conscious patients than in the two other patients groups may be interpreted in terms of limited central capacity: when subjects do perform the global deviance detection task they have to process this attribute without responding to the local deviance, which is in opposition to global deviance in half of the trials. Therefore, given the limited serial property of conscious content, they would be able to consciously process only a single dimension (global deviance). As a consequence, the ERP component following the MMN would be predicted to be smaller in such conscious subjects performing the task, than both in non-conscious patients in whom only automatic responses to local deviance would be observed, and in conscious but cognitively impaired patients whom central resources would be captured by the processing of local deviance. This hypothesis is strengthened by two elements: the anterior positivity following the MMN in the local effect contrast (local deviant versus local standard trials) overlap in time with the beginning of the P3 complex observed in the global effect contrast (global deviant versus global standard trials). Moreover, we recently provided evidence in support of a two-stage model of accumulation of evidence during auditory oddball paradigms (Pegado et al., 2010). According to this model and experimental data, late portion of the MMN (160–220 ms) and subsequent components (including the following positivity) are interpreted as central stages of processing. Assuming that this interpretation is valid, and that the absence of a P3a response to local deviance in conscious subjects reflect their conscious engagement in the processing of an orthogonal dimension of the stimuli (global deviance), one may well understand the presence of this ERP component in the MCS group (conscious processing of local deviance due to cognitive impairments), but may wonder why this ERP component would be observed in the VS patients group? While speculative, we may propose that this ERP component could reflect a form of unconscious exogenous attention which may be preserved in some non conscious patients, and which would not be an index of reportable conscious contents. Indeed, in conscious controls an increasing set of evidence point to the existence of such unconscious deployment of attentional resources, for instance in response to salient stimuli (Koch & Tsuchiya, 2007; Mulckhuyse & Theeuwes, 2010).

Lastly, a clear difference across the four groups was the presence of a late anterior negativity in the MCS and VS patients groups, while no late effect was observed in the two conscious subjects groups (controls and conscious patients). Interestingly, we previously observed such a late effect both in one MCS patient, and in several conscious controls under an attentional manipulation preventing them from being conscious of the global regularity (see groups 2 and 3 of Bekinschtein, Dehaene, et al., 2009, and patient MCS#4 in the same study). We proposed that such a late local effect could reflect that these individuals: “processed consciously the local deviant trials, yet without being able to detect the existence of a global regularity”. In other terms, we hypothesized that given the limited capacities of conscious access (Dehaene & Naccache, 2001), a subject who is representing consciously representations of stimuli in terms of global deviance (e.g.: conscious control subject) would not represent consciously local deviance of stimuli, and therefore would not show late local effects. In contrast, a conscious subject unable to represent global deviance could show such late local effects. This line of interpretation of this effect would make use of the very same logic as for the P3a response (see above). This component may therefore reflect deeper cognitive integration of the local deviance than MMN. Further studies may use this late local effect to better discriminate across VS patients those with deeper perceptual integration of the environment.

4.4. An early ERP marker of cognitive expectations

While this work was driven by the exploration of ERP responses to both global and local deviances of the stimuli, we discovered an unexpected ERP response. We observed that prior to the delivery of the fifth sound, - which was conveying simultaneously information of local and global deviance of the current trial -, conscious controls showed a clear slow negative drift beginning with the onset of the first tone of the series, and closing with the early (~200 ms) processing of the fifth tone. As we noted above (see Results section) this ERP effect is extremely suggestive of the classical ‘Contingent Negative Variation’ (Walter et al., 1964) which has been initially described in a paradigm where the subjects are instructed that a warning stimulus followed by a target stimulus will be delivered on each trial, with a random or fixed stimulus onset asynchrony (SOA). Processing of the warning stimulus elicits a CNV which terminates when the target stimulus is delivered and processed. CNV has been reported in various motor and cognitive tasks, and has been reported to correspond to the activation of a large network implicating in particular frontal cortices (Gomez, Flores, & Ledesma, 2007; Niedermeyer, 2003; Rosahl & Knight, 1995). CNV is affected by manipulations of attention and motivation (Rockstroh, Elbert, Birbaumer, & Lutzenberger, 1982). In the present study, the negative drift showed an anterior negativity scalp topography reminiscent of the CNV, and the regular structure of our stimuli encouraged expectative processes of the fifth sound once the first sound was perceived. As in classical ‘S1–S2’ CNV paradigms, a first stimulus announced the occurrence of the second and crucial stimulus on which a task had be performed (Walter et al., 1964). Moreover, we could identify this CNV component only in groups of conscious subjects (controls and patients), further corroborating the cognitive nature of this ERP component. At the individual level, we could isolate a CNV in all conscious controls, and in the majority (61%) of conscious patients’ recordings. Capitalizing on these premises, we then sorted all patients’ recordings according to the presence of this CNV (29 CNV+ and 36 CNV− recordings). We then recomputed the local and global effects in each of these two groups. While both groups showed early and late local effects, we observed a clear global effect in the CNV+ group only. Note that this is not a trivial result given that no global effect could be observed at the group level in any of the 3 groups of patients. As discussed about the late local effect, this CNV component may help to distinguish among MCS and VS patients those who display a richer mental life. At a theoretical level, relations prevailing between CNV and consciousness are not very well documented. As far as we could review the literature, a single observation on two comatose patients reported the presence of a component resembling CNV (Dolce & Sannita, 1973). By reporting here experimental data showing that multiple VS patients displayed a clear CNV in the absence of any clinical and electrophysiological markers of consciousness, we provide strong evidence in favor of the existence of non-conscious expectative processes. As for the exogenous deployment of attention by salient stimuli, it seems that expectative processes, driven by auditory regularities delivered within a short time-window compatible with unconscious echoic memory system, exist. One limitation of our study relies in the fact that both local and global deviance information were conveyed by the same event. Therefore, it is not easy to distinguish between local and global regularities expectations, and in consequence between conscious and unconscious forms of expectation. Future works may use this CNV approach to distinguish between conscious and non-conscious forms of expectations, and to test for their independence.

4.5. *Learning effects*

This paradigm also offered us the opportunity to look for learning effects by contrasting ERPs elicited by the very same stimuli, according to the period during which they were delivered. Interestingly, these effects could reflect attentional and/or strategical learning effects. Indeed, they are not confounded with time given that the learning periods were distributed over the 8 experimental blocks. Note also that the first learning effect occurring well before the onset of the fifth sound cannot be explained simply by a difference in probabilities of the first sounds which were identical across both conditions. Moreover, the observation that only conscious and MCS subjects showed this early learning effect is coherent with an attentional/strategical interpretation. Indeed, the single VS patient showing this early effect was probably conscious during recording: she presented both a learning and a global effects, and recovered univocal signs of consciousness 3 days after the recording session (see Faugeras et al., 2011). It is noteworthy that when considering the presence of either the global effect or the early learning effects, one can discriminate conscious patients (conscious and MCS patients) from VS patients with a similar and almost perfect specificity (see above), and with a stronger sensitivity (39% versus 27%) than when using the global effect alone. It is possible that spectral analyses enrich the detection of these learning effects which may correspond to sustained cognitive states rather than to events locked in time with stimuli or responses. Future analyses may confirm this hypothesis.

4.6. *Conclusion*

The ERP ‘global effect’ can be used as a highly specific marker of consciousness in non-communicating patients with a specificity close to 100%. In the presence of a global effect in an individual clinically diagnosed as non-conscious (e.g.: VS), one has to question the clinical diagnosis and to carefully observe the patient. Future works taking advantage of real-time analysis of EEG signal, and combining several electrophysiological measures of brain activity may increase the sensitivity of this index of consciousness and may go beyond diagnostic-oriented measures of brain activity, to enable communication in conscious but impaired patients through real-time brain computer interfaces.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuropsychologia.2011.12.015.

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Annexe 5

Chapter

7

Neurology of consciousness impairments

Benjamin Rohaut, Frédéric Faugeras, and Lionel Naccache

SUMMARY

Probing consciousness in non-communicating patients at bedside can be very challenging. In this chapter, we describe some of the key goals, caveats and pitfalls of the evaluation of consciousness in non-communicating patients. First, we will address the importance of neurological and behavioral examination, and then briefly outline the current developments of functional brain-imaging tools able to provide important additional evidence. Current approaches include both: (i) active paradigms in which a patient is asked to perform a specific cognitive task; (ii) "resting state" conditions in which the spontaneous patterns of brain-activity can be instructive of patients conscious state; and (iii) passive paradigms in which cortical functional connectivity can be explored by recording, for instance, EEG in response to focal transmagnetic stimulation (TMS) pulses.

Introduction

In this chapter, we intend to summarize the key goals, caveats, and pitfalls of the evaluation of consciousness in non-communicating patients, and in particular in awake patients in whom this issue is the most difficult to solve. Distinguishing minimally conscious (MCS) and conscious states from vegetative (VS) and comatose states can be extremely challenging at bedside. We will first address the importance of neurological and behavioral examination, and then briefly outline the current developments of functional brain-imaging tools able to provide important additional evidence. Far from being systematically categorical, we will also try to provide the reader with the current weights of (un)certainty associated with each clinical sign or neurophysiological measure mentioned in this chapter.

Caveats and pitfalls of consciousness examination

Examining an awake, eyes open, and yet non-interactive patient with no clear evidence of consciousness can be a very awkward situation. For instance, both MCS and VS patients can perform behaviors such as laughing, crying, grimacing, and they can demonstrate withdrawal movements to nociceptive stimulation. All these rich behavioral, and sometimes emotional, manifestations are difficult to interpret in relation to the conscious status of the patient, and the observers can easily overestimate them as univocal evidence of a voluntary conscious state. This problem is frequent in clinical practice, and can be the source of contradictory interpretations within a team of caregivers, and with patients' relatives. Assessing consciousness and/or residual cognitive abilities of a disorders of consciousness (DOC) patient obviously requires neurological expertise. We will adopt here the classical definition of consciousness as a "state of full awareness of the self and one's relationship to the environment" [1].

Do not overestimate consciousness

Visual fixation

Visual fixation is defined by at least two consecutive ocular saccades to a target followed by a fixation longer than two seconds (see for instance the Full Outline of UnResponsiveness (FOUR-score) [2] and the revised version of the Coma Recovery Scale (CRS-R) [3] (see Tables 23.2 and 7.1). It is admitted that visual fixation does not require conscious access to the visual target, given that it can be observed for instance in some patients with cortical blindness ("blindsight" phenomenon), but it is still not clear

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Table 7.1 Coma Recovery Scale – Revised

- **AUDITORY FUNCTION SCALE**
  4 – Consistent movement to command*
  3 – Reproducible movement to command*
  2 – Localization to sound
  1 – Auditory startle
  0 – None
- **VISUAL FUNCTION SCALE**
  5 – Object recognition*
  4 – Object localization: reaching*
  3 – Visual pursuit*
  2 – Fixation*
  1 – Visual startle
  0 – None
- **MOTOR FUNCTION SCALE**
  6 – Functional object use**
  5 – Automatic motor response*
  4 – Object manipulation*
  3 – Localization to noxious stimulation*
  2 – Flexion withdrawal
  1 – Abnormal posturing
  0 – None/flaccid
- **OROMOTOR/VERBAL FUNCTION SCALE**
  3 – Intelligible verbalization*
  2 – Vocalization/oral movement
  1 – Oral reflexive movement
  0 – None
- **COMMUNICATION SCALE**
  2 – Functional: accurate**
  1 – Non-functional: intentional*
  0 – None
- **AROUSAL SCALE**
  3 – Attention
  2 – Eye opening without stimulation
  1 – Eye opening with stimulation
  0 – Unarousable

** Denotes emergence from minimally conscious state (MCS).
* Denotes MCS.

whether visual fixation needs primary visual cortex, or may be mediated through the superior colliculus pathway [4]. In the CRS-R the presence of this behavior rules out the diagnosis of VS, while it is not the case according to the Multi-Society Task Force on the persistent vegetative state (PVS) [5], and to the Royal College of Physicians' report [6]. Accordingly, a recent PET study did not report any difference in brain metabolism between VS patients with preservation of visual fixation and VS lacking this behavior. Similarly, both groups shared the same 1-year outcome [7]. From a theoretical point of view, a long-lasting intentional behavior is a gold standard criterion of consciousness [8]. As a consequence, one may consider that a fixation sustained over several seconds belongs to this category of conscious behaviors. However it is highly notable that fixation is dependent of the continuous presence of the visual target, and may therefore correspond to a continuously stimulated visuomotor reflex, rather than to a long-lasting internally generated behavior. A patient able to fixate a target, and to maintain fixation on instructions even after the disappearance of the stimulus, and even if presented with competing stimuli, would demonstrate a much stronger evidence of conscious processing.

Blink to threat

In contrast with auditory startle – or maybe also of visual fixation – blink to visual threat (BVT) probably requires cortical processing [9–11]. Functional integrity of primary visual cortex is a mandatory stage, but note that patients with cortical lesions located away from cortical pathways (e.g., frontal or parietal) can lose BVT [10]. The Multi-Society Task Force stated that the diagnosis of persistent VS (PVS) should be extremely cautious in the presence of BVT [5]. However, BVT is not a criterion taken into account to distinguish VS from MCS [12]. In terms of consciousness recovery, BVT does not seem to be a predictor of a better outcome [11]. Therefore, while BVT requires richer cortical processing than visual fixation, it does not guarantee a patient to be conscious, or even minimally conscious. However, presence of a BVT requires the examiner to be even more cautious to look for additional signs of cortical integrity, and for the presence of more reliable signs of consciousness. To close with that sign, note that it is highly important not to confound it with corneal reflex elicited by an air puff caused by target motion.

Oro-facial behaviors

Oral reflexes such as chewing, teeth grinding, or swallowing are not problematic but other behaviors such as facial movements (smiles or grimaces), tears, grunting, or groaning sounds could be easily considered as conscious behavior. In this case, a possible adapted emotional behavior should be carefully searched for, and for example if a patient cries only in the presence of one of his or her relatives, one has to look for the presence of more univocal signs of MCS or of conscious state. Clearly, current knowledge is insufficient to provide any strong claim about these complex and sometimes specific emotional responses.

Additional signs

Noxious or noisy stimuli can elicit arousal responses, with autonomous reaction (e.g., increases of respiration and heart rates), grimaces or limb movements, and cause the extensor or flexor withdrawal of a limb. None of these signs should be confounded with a conscious behavior. Similarly, gaze or head orientation toward a loud sound is considered as reflex, and does not exclude VS [6,12]. In the same vein, grasping reflex and triple withdrawal should not be confounded with intentional movements.

Do not miss consciousness

While it is crucial not to overestimate consciousness (the “false positive” issue), it is even more dramatic to miss conscious patients. However, many factors can lead to such an error. Consider a conscious but non-communicating patient. On the basis of clinical observation and testing, consciousness is never probed as a “pure” and isolated process but rather in relation to many distinct cognitive abilities, to sensorimotor processes, and to mental contents [13]. Therefore, trivial or subtle impairments in any of those abilities, processes, or contents may lead to the absence of clinical evidence of conscious processing in a conscious but severely disabled patient. Illustrations of “trivial” impairments correspond to deaf, blind, or paralyzed conscious patients. Note that even these “trivial” or “easy” cases are not that easy to deal with. An astonishing study on locked-in syndrome (LIS) patients reported that the mean time of LIS diagnosis since the initial event was around 2.5 months [14]. One has to take into account that at the initial stage of a massive brainstem stroke, patients are usually in a genuine comatose state during a variable period. Recovery of consciousness from this initial comatose state may be missed if clinical evaluations are not repeated very regularly. Therefore, this long diagnostic delay emphasizes the need of repeating these evaluations, and of varying the ways of assessing consciousness.

Visual pursuit

When looking for visual pursuit, the use of the patient’s own eyes (and even own face) as a visual target seems to be the most powerful stimulus, probably due to self-referencing (e.g., the “cocktail party effect” which corresponds to the powerful ability to react to one’s own name when heard in a complex auditory scene) [15]. Indeed, the utilization of a mirror to detect visual pursuit has been shown to be more sensitive than any other visual stimuli (other faces, contrasted, or colored targets) [16]. As mentioned below, visual pursuit is one of the most informative signs to classify a patient as MCS or conscious.

Cognitive impairments

Less trivial situations are encountered in DOC patients suffering from aphasia, or from massive anterograde amnesia, or severe dysexecutive syndrome impacting attentional, working memory, and strategic abilities. In many of the clinical tests used with DOC patients, one may miss some form of conscious processing. Obviously, there is no easy solution to this point. However, a rigorous examination using both verbal and non-verbal instructions and stimulations (e.g., imitation or automatic behavior) may help to overcome some of these limitations. Additionally, systematic assessment of any possible movement (hands, feet, eyes, blinks, mouth and tongue movements) will maximize the probability to detect an intentional response. Repetition of clinical evaluations is particularly important in the “acute” stage (first days and weeks), given the presence of frequent and major fluctuations in arousal and also possibly in consciousness, in particular in MCS patients.

Neglect

Attentional disorders such as spatial hemi-neglect – observed in patients with a non-dominant hemispheric lesion – could explain both perceptual difficulties (culminating in the neglect of instructions delivered in the neglected hemi-space) and behavioral responses impairments (motor neglect) in the absence of any central or peripheral motor neurons dysfunction. Patients have to be stimulated and observed from both sides (right and left).

Aphasia

Patients with dominant hemispheric lesions could be expected to have language impairments. In this case intentional and voluntary behaviors should be tested using non-verbal communication and instructions. This consideration is not yet implemented in standard behavioral scales, but most verbal commands could be delivered by gestural description. For example the examiner can show the movement of a handshake to the patient with one hand, while testing the patient’s response with the other hand [17].

Taken together, these elements contribute to explain that up to 40% of patients considered as VS demonstrate univocal evidence of MCS when examined by expert teams used to current detailed scales [18].

Finally, one has to be aware of the possible persistence of sedative agent effects. Electroencephalography and, most importantly, pharmacological measurements and pharmacological antagonistic tests (e.g., for benzodiazepines and morphinic agents) are sometimes extremely valuable here, in particular in comatose patients. Similarly one has to systematically check body temperature and hemodynamic constants when examining a DOC patient, and in particular when examining a comatose patient and a suspicion of brain death.

Overview of clinical and behavioral assessment of consciousness

Consciousness first requires a minimal level of arousal, the absence of which is observed in comatose states.

Arousal and basic neurological assessment

Arousal depends on the ascending arousal system distributed within the tegmentum of the upper pons and midbrain, and in paramedian diencephalic structures along with the basal forebrain. These structures widely project onto the cortex including the thalamo-fronto-parietal network which plays a major role in consciousness, as theorized for instance in the conscious "global workspace" model [19]. Therefore coma can result from diffuse bihemispheric lesions (e.g., anoxia, trauma) or dysfunction (e.g., status epilepticus), or from focal brainstem lesions affecting in particular the pontomesencephalic tegmentum, or paramedian diencephalic structures bilaterally.

In front of a comatose patient, neurological examination aims at three major goals: (1) to confirm the diagnosis of comatose, and therefore to discard differential diagnoses such as locked-in syndrome, for instance; (2) to estimate the functional depth of the comatose state from profound and poorly reversible comatose to "diencephalic" comatose associated with a better prognosis of consciousness recovery; and (3) to provide potential cues to the etiological diagnosis (e.g., presence of discrete palpebral myoclonus in a status epilepticus; fever and meningitis syndrome in an acute meningo-encephalitis). Here, we will only underline the "functional depth" issue: basically, comatose is probably the clinical condition in which Hughlings Jackson's seminal concept of the central nervous system (CNS) described as a "hierarchical vertical axis" is the most relevant [20]. According to Jackson theory, the higher a CNS region is, the more it controls and inhibits the CNS regions located below it, and the weaker it is to CNS "aggressions." This famous conception was the first to provide a satisfactory account of the positive signs secondary to a CNS lesion (e.g., disinhibition of medulla reflexes associated to primary motor cortex lesion). As a consequence, examination of brainstem reflexes in relation to the vertical location of their neural substrates within this hierarchical axis plays a major role: the lower reflexes are usually the most resistant, and one can frequently observe a gradient of reflexes preservation. This "neo-jacksonian" view inspired for instance the scoring of the famous Glasgow Coma Scale and its variants including brainstem reflexes scoring (such as the Glasgow–Liège scale) or the more recent FOUR-score (see Tables 7.2 and 23.2): the upper reflexes are more weighted than the inferior ones, and the scoring of motor reactivity to stimulation also follows this supero-inferior gradient: a decortication response is scored better than a decerebration response. As a matter of fact it is extremely rare to observe the presence of oculo-cephalic reflexes in a comatose patient in whom oculo-cardiac reflex would be abolished. Combining all these observations with the inspection of pupil diameter, reactivity, and symmetry, and with the spontaneous breathing pattern (e.g., from Cheynes–Stokes dyspnea to apneustic or ataxic respiration) usually allows definition of the "functional depth" of comatose, and to monitor it

Table 7.2 Glasgow Coma Scale

- Eye response
  4 – eyes open spontaneously
  3 – eyes opening to verbal command
  2 – eyes opening to pain
  1 – no eyes opening
- Motor response
  6 – obeys commands
  5 – localizing pain
  4 – withdrawal from pain
  3 – flexion response to pain
  2 – extension response to pain
  1 – no response to pain
- Verbal response
  5 – oriented
  4 – confused
  3 – inappropriate words
  2 – incomprehensible sounds
  1 – no verbal response

across time in a given patient. When this detailed clinical examination does not fit with this functional gradient view, one has to look for focal lesions within the brainstem, or for additional factors which may interfere (e.g., drugs, metabolic dysfunctions).

Consciousness assessment

A more subtle alteration of consciousness is the vegetative state, which is characterized by preserved wakefulness [21] – even if circadian rhythms may not be strictly normal [22] – in the absence of any purposeful behavior and of any sign of intentional reactions to the external environment. Note that VS is, by definition, a clinical syndrome and not a specific condition. For this reason, and in order to avoid too radical interpretations of patient's cognitive state only based on behavioral observations, a group of experts recently proposed the 'Unresponsive Wakefulness Syndrome' expression to describe VS [23]. The mere existence of VS demonstrates that wakefulness and consciousness can be dissociated, and therefore that they cannot be identified one with another.

Consequently, several scales have been created in order to distinguish VS patients from MCS patients. All these scales enable the clinician to administer various language, auditory, visual, somatosensory, and noxious stimuli and judge whether a patient's responses are indicative of conscious processing. Stimulations have to be repeated within the same examination session, in particular when spontaneous behavioral fluctuations are frequent. It is also important to gather all sources of observational evidence, including various caregivers and relatives who deserve a special consideration: while not being experts of behavioral assessment and being frequently the most motivated to interpret the behavior of their companion as conscious, they are also the most meaningful, or as Damasio phrases it: the most "emotionally competent" to the patient. It means that they are sometimes the most active stimuli to elicit a patient's richest behaviors. It is therefore sometimes useful to include the relatives to some stages of consciousness assessment. Furthermore, confounding variables (sedation, noisy environment, physical limitations) must be reduced to a minimum.

All these scales share a common design, combining: (1) items which appreciate coma exit [e.g., item 2 of the Wessex Head Injury Matrix (WHIM); arousal scale of the Coma Recovery Scale Revised (CRS-R)], with (2) items (see Table 7.1) probing purely reflexive behaviors integrated at a brainstem level and indicative of a vegetative state if isolated despite repeated assessment (e.g., item 3 of the WHIM, or item 2 of the auditory function scale of the CRS-R which imply integrity of the colliculi and the tectospinal tracts), and with (3) items exploring behaviors requiring cortical integration and sustained activity, properties which are considered as specific to conscious processing (item 18 of the WHIM or items 2 and 3 of the vision function scale of the CRS-R which imply integrity of parietal and frontal eye fields area).

Note that a recent study explored a clinical sign previously described and emphasized by Plum and Posner as a marker of preserved cortical integration. The authors assessed the fast nystagmic return to mid-position of the eyes after ipsilateral tonic deviation towards the cold water-irrigated ear during testing of the oculovestibular reflexes [24]. This saccadic return – probably mediated by a long-range fronto-parietal cortical network – predicted consciousness recovery in a group of 26 clinically defined VS patients. Thirteen out of these 26 patients ultimately recovered consciousness. All patients who recovered consciousness presented a fast-component of nystagmus compared with only one of 11 patients who remained unconscious.

Using cognitive neuroscience to look for consciousness in patients

A complementary approach to clinical neurology originates from cognitive neurosciences of consciousness. Although the issue remains debated, two decades of experimental and theoretical work have led to the characterization of psychological and neurophysiological attributes that may be unique to conscious processing. Many cognitive processes may occur unconsciously either in conscious subjects, in visual neglect patients or related patients, and in non-conscious patients [25–27], reaching such complex levels as abstract semantics, phonological or emotional processing. Still, three properties seem to be exclusively associated with conscious processing of reportable mental contents [19]: (1) active maintenance of mental representations in working memory; (2) strategic processing; and (3) spontaneous intentional behavior. Similarly, while unconscious processing may engage multiple isolated cortical areas, neural signatures of conscious processing are defined by late and long-lasting brain activations that mobilize long-distance coherent thalamo-cortical networks, particularly involving bilateral prefrontal, cingulate, and parietal areas [25,28].

On the basis of these studies, original experimental "active" paradigms can therefore be designed in order to improve our ability to diagnose consciousness in non-communicating patients, beyond clinical evaluations. For instance, at the behavioral level, Bekinschtein and colleagues [29] capitalized on the working memory property mentioned above, and used an eyeblink conditioning paradigm in which a tone stimulus can be paired with an air puff delivered on the cornea. Delayed conditioning – where the conditioned stimulus and the unconditioned air puff overlap in time – does not require conscious processing of the stimuli. In contrast, trace conditioning where a temporal gap is inserted between the two stimuli seems to require conscious processing in working memory [30]. Interestingly, they showed that some clinically defined VS patients were able to demonstrate both conditioning and trace conditionings. Functional brain-imaging approaches are also emerging [31]. For instance, Owen and colleagues (32) probed with functional magnetic resonance imaging (fMRI) the active maintenance of task-instructed cognitive tasks, such the ability to perform motor or spatial imagery tasks for an extended duration of 30 seconds (see Figure 7.1). Using this approach on 54 patients, they could identify five patients able to willfully modulate

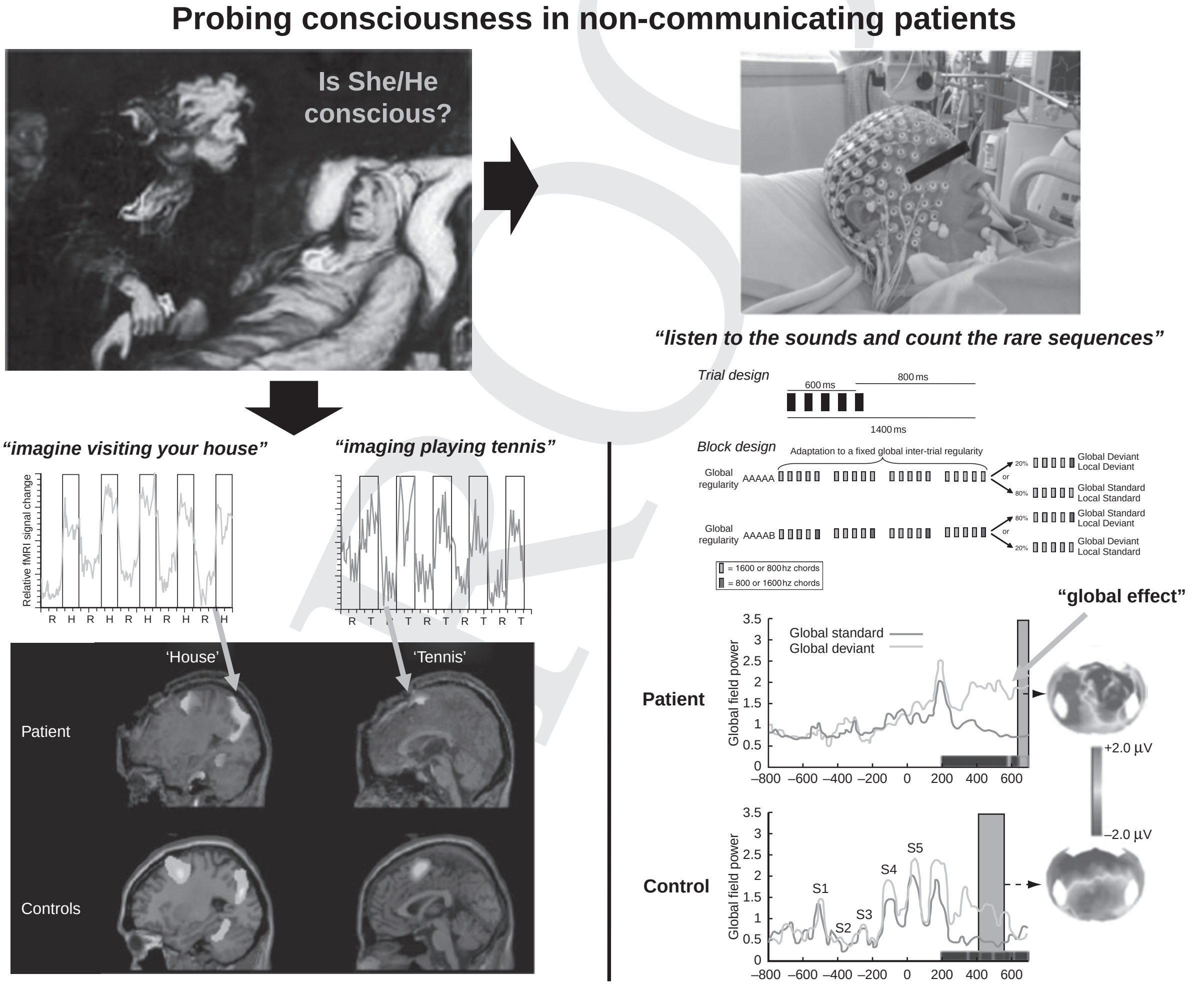

Figure 7.1 Two recent illustrations of active paradigms using functional brain imaging (EEG and fMRI) to probe consciousness in non-communicating patients. The mental navigation and mental motor imagery tasks designed by the group of Owen (left) allow the detection of sustained fMRI BOLD activations in cortical networks specific to each of these two mental imagery tasks [32]. The global regularity auditory task designed by the group of Naccache [42] allows the detection of late and sustained P3-like EEG responses when patients detect the occurrence of global regularity violations. In these two paradigms, the presence of a significant effect is highly suggestive of conscious processing.

their brain activity [33]. Among these five patients, two were clinically classified as VS. In one clinically MCS patient, fMRI could be used to define an arbitrary code and communicate a single piece of information (a yes/no answer), while such a communication was not possible behaviorally.

In parallel to such fMRI experiments, EEG paradigms may constitute a highly promising research direction for at least two reasons. First, EEG is a time-resolved tool able to sample brain activity at the millisecond scale. This offers a unique opportunity to monitor the flow of consciousness and eventually to interact with the patient in real time. Second, given that EEG is a non-invasive technique, has a relatively low cost and can be recorded at bedside, one may ultimately design dedicated systems for recurrent and even continuous daily recording of brain activity in patients. In that respect, EEG monitoring seems more likely to truthfully reflect VS and MCS patients' complex fluctuating states than a single fMRI scan lasting a few tens of minutes. Schnakers and colleagues showed the utility of using active EEG paradigms to probe voluntary brain responses to stimuli. They could confirm the presence of conscious processing in a locked-in syndrome patient and in clinically defined MCS patients [34].

Active paradigms are important because they provide a way to probe various cognitive processes by looking for their specific neural signatures. However, this very same property confers a severe limitation: if for any reason the patient does not engage in the cognitive performance requested by the experimenter, then the test will fail to identify this patient as conscious even if she or he is conscious. If the patient is not awake during the task (e.g., confusional states, sleep cycles), or is conscious but cognitively impaired (aphasia, amnesia, poor working memory, dysexecutive syndrome), or refuses to obey the instructions, active paradigms will fail to diagnose this conscious patient as conscious.

For all these reasons, it is therefore useful to develop additional neurophysiological measures which could escape some of the limits of active paradigms. One promising path of research consists in recording brain activity in the absence of external stimulation. This approach is grounded on the seminal work of Raichle's group on the "resting state" or "default mode" (DM) networks aims at exploring the spontaneous patterns of brain activity [35]. One of these DM networks include mesial cortical areas, including the precuneus and the posterior cingulate cortex and seems to be related to self-consciousness and to introspective processes. Some key regions of this network may contribute to a general "projective system" enabling the individual to escape from immediate contingencies, e.g., projection in time (past and future), in space (mental navigation), and in mind (theory of mind) [36]. Functional MRI recordings of these DM networks seem to be informative about the level of consciousness in non-communicating patients [37]. It is important to note that while recording of resting state activity is not complex as compared with active paradigms, the selection of the most relevant analyses to be done on these raw data still remain a subject of research. Resting state measurements were initiated with fMRI but recent electrophysiological works pave the way to explore more finely these dynamics [38].

Lastly, a very elegant method combining EEG and TMS offers an easy way to probe the functionality of long-distance cortico-cortical networks at bedside without relying on a specific cognitive process. The principle consists in recording EEG with a fairly good spatial sampling over the whole cortex (from 32 up to 256 electrodes) immediately after the delivery of a single pulse of TMS over a local region of the cortex. By observing both early local, but most importantly late and sustained global responses, in particular over fronto-parietal regions, one may probe the existence of a functional "global workspace" network. First applications of this method during sleep [39], under midazolam anesthesia [40], and in DOC patients [41] strengthen its ability to isolate neural correlates of long-distance coherent cortical activities related to conscious states.

The 'local global' test of consciousness

We will now focus on one "active" paradigm which provides a very specific (but not a very sensitive) way to probe consciousness in patients. We recently designed an auditory paradigm that evaluates the cerebral responses to violations of temporal regularities [42]. Local violations due to the unexpected occurrence of a single deviant sound amongst a repeated train of standard sounds led to an early response in auditory cortex, the mismatch negativity (MMN) ERP component, independent of attention and of the presence of a concurrent visual task. On the other hand, global violations, defined as the presentation of a rare and unexpected series of five sounds, led to a late and spatially distributed response that was only present when subjects were attentive and aware of the violations (P3b ERP component). We could detect the global effect in individual subjects using fMRI and both scalp and intracerebral event-related potentials. Since the original publication [42], we reported the results obtained in 73 recordings of non-communicating patients (32 recordings in MCS, 28 VS, and 13 in conscious patients) and confirmed that only conscious individuals (MCS or CS) presented a global effect (see Figure 7.1). When focusing on the group of VS patients, we confirmed the absence of global effect in the vast majority of patients, but identified two patients showing this neural signature of consciousness [43,44]. Interestingly, these two patients showed unequivocal clinical signs of consciousness within the 3–4 days following ERP recording, strongly suggesting they were misclassified as VS due to limitations of clinical examination. Taken together, these observations were highly suggestive that the global effect might be a signature of conscious processing, although it can be absent in conscious subjects who are not aware of the global auditory regularities.

Conclusion

In this non-exhaustive overview, we tried to emphasize the crucial importance of expert and informed clinical examination. Currently, up to 40% of patients may be misdiagnosed, most often considered as VS while they show univocal behavioral evidence of conscious or minimally conscious states (e.g., sustained visual pursuit in the mirror test of the CRS-R). It is probably the case that such a high error rate also reflects a prevailing opinion that being able to distinguish VS from MCS does not impact so much on the way we manage these patients. While this opinion highlights our weak therapeutic efficacy in these patients, in particular in chronic situations, we think it is important to remember that recognizing an MCS from VS is crucial for the patient, and for the relatives and caregivers. Note also that MCS patients seem to have a better functional prognosis outcome than VS patients [45]. Several new and valuable clinical scales and procedures are now increasing the power and standardization of consciousness probing in these patients. In parallel to this emphasis on clinical observation, we also tried to briefly show some of the very promising functional brain imaging tools (in particular EEG, fMRI) taking advantage of the psychological properties of conscious processing to directly look for them in brain activity rather than in behavior. We think such tools will be integrated with the clinical assessment in these difficult situations. Finally, in identified conscious but non-communicating patients, current developments of EEG-based brain–computer interfaces may constitute a major therapeutic improvement by restoring to these patients the ability to “action their mind.”

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Table des illustrations

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Glossaire

AG: *angular gyrus;* gyrus angulaire

aSTG: *anterior superior temporal gyrus*; partie antérieure du gyrus temporal supérieur

AVC: accident vasculaire cérébral

DLPFC: *dorso-lateral prefrontal cortex*; cortex préfrontal dorso-latéral

EEG : électroencéphalographie

FG : *fusiform gyrus* ; gyrus fusiforme

GNW : *Global Neuronal Workspace* ; espace de travail conscient

IRMf: imagerie par résonance magnétique fonctionnelle

IFG: *inferior frontal gyrus*; gyrus frontal inferieur

LIFG: *left inferior frontal gyrus*; gyrus frontal inférieur gauche

LPC: *Late positive component*; composant positive tardive ou P600

MCS : *Minimally Conscious State* ; état de consciente minimale ou état pauci relationnel

MEG : magnétoencéphalographie

MTG: *middle temporal gyrus;* gyrus temporal moyen

PE: potentiel évoqué

PC: *posterior cingulate gyrus;* gyrus cingulaire postérieur

SFG :*Superior frontal gyrus* ; gyrus frontal supérieur

SMG: *supramarginal gyrus;* gyrus supra-marginal

SOA: *stimulus onset asynchrony;* asynchronie entre le début des stimuli

SRAA : substance réticulée activatrice ascendante

TMS : *transcranial magnetic stimulation* ; stimulation magnétique transcrânienne

VMPFC: *ventromedial prefrontal cortex*; cortex préfrontal ventro-médial

VS : *Vegetative State ;* état végétatif ou état d’éveil non répondant

Rohaut Benjamin – Thèse de doctorat - 2015

Résumé :

L'étude de fonctions cognitives aussi complexes que le langage, la conscience et a fortiori leurs relations, constitue un vrai défi aux confins de la médecine (réanimation, anesthésie, neurologie) et des neurosciences cognitives. Le traitement sémantique procure à nos expériences perceptuelles un niveau de représentation abstrait, permettant une variété de fonctions conceptuelles telles que la reconnaissance d'objet, la cognition sociale, ou le langage. Dans ce travail de thèse, nous avons voulu explorer les relations entre le traitement sémantique verbal et la conscience en adoptant une double approche : d'une part en étudiant des sujets sains en condition de perception consciente et inconsciente (en utilisant une technique de masquage visuel), et d'autre part en étudiant des patients présentant un trouble de la conscience en modalité auditive. Au travers de ce travail, nous apportons des arguments en faveur de l'existence de représentations sémantiques verbales inconscientes. Nous proposons également que les deux signatures cérébrales de ces traitements sémantiques observées en potentiels évoqués (N400 puis LPC/P600) puissent s'intégrer dans un modèle à deux temps : premier temps inconscient (correspondant à la N400), puis second temps conscient (correspondant à la LPC/P600). En explorant les différences entre traitement conscient et non conscient, nous montrons que le traitement sémantique non conscient est lui aussi sensible aux influences descendantes conscientes, ce qui réfute une conception strictement automatique de la cognition inconsciente. Nos résultats apportent également un nouveau regard sur les mécanismes de résolution d'ambiguïté sémantique pouvant laisser suggérer des différences entre hémisphères. L'exploration des capacités cognitives de haut niveau telles que le traitement sémantique verbal, chez des patients présentant un trouble de la conscience, devrait permettre des avancées notables dans leur prise en charge.

Mots clés : [conscience ; sémantique verbale ; amorçage sémantique ; masquage visuel ; trouble de la conscience ; potentiels évoqués ; N400 ; LPC ; P600]

Relations between semantic processing & consciousness: ***A behavioral and neurophysiological approach in healthy volunteers and brain-injured patients***

Abstract:

The study of cognitive functions so complex such as language and consciousness, and of their interactions, is a challenge at the boundaries between medicine (intensive care, anesthesia, neurology) and cognitive neuroscience. Semantic processing provides our perceptual experiences with a level of abstraction allowing a variety of conceptual functions such as object recognition, social cognition, or language. In this thesis, we explored the relationships between the verbal semantic processing and consciousness using a double approach: first, by studying healthy subjects in conscious and unconscious condition (using visual masking), and secondly by studying patients with disorders of consciousness in the auditory modality. Through this work we provided empirical evidence of unconscious semantic representations. We then proposed that the two main brain signatures of semantic processing observed in ERPs (N400 and LPC / P600) could be integrated in a two stages model: a first unconscious stage (corresponding to the N400), followed or not by a second stage of processing corresponding to conscious semantics (LPC / P600). Exploring the differences between conscious and nonconscious processing, we showed that nonconscious semantic processing is sensitive to conscious top-down influences. These results refute a strictly automatic conception of unconscious cognition. Our results also shed new light on the respective roles of the two hemispheres in the resolution of semantic ambiguity. The exploration of high-level cognitive abilities, - such a verbal semantic processing - in patients affected with disorder of consciousness should enable significant advancements in their medical management.

Keywords: [consciousness; verbal semantics; semantic priming; visual masking; disorders of consciousness; event related potentials; N400; LPC; P600]