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THE ROLE OF THE MEDIAL TEMPORAL LOBE IN BINDING LYRICS AND MELODIES :

A neuropsychological and neuroimaging approach

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Because a major sixth always reminds me where I come from.

Résumé

Les chansons lient naturellement des mélodies à des paroles. Elles représentent l'une des formes les plus utilisées de l'expression musicale. De façon intéressante, les chansons nécessitent l'intégration simultanée d'informations verbales (les paroles) et d'informations musicales (la mélodie) pour former une seule trace mnésique. Le lobe temporal médian a été identifié comme région clé pour la mémoire épisodique et en particulier pour le processus de binding, qui consiste en la liaison de plusieurs éléments d'un souvenir. Néanmoins, les mécanismes par lesquels le cerveau réalise la liaison entre paroles et mélodies dans la mémoire des chansons restent peu connus. L'objectif de cette thèse est de montrer le rôle du lobe temporal médian dans le processus de binding de paroles et mélodies pour la création d'un souvenir unifié d'une chanson. Premièrement, nous avons étudié les effets d'une sclérose unilatérale de l'hippocampe associée à une épilepsie du lobe temporal sur le processus de mémorisation des chansons en IRM fonctionnelle (**étude 1**). Les patients avec une sclérose de l'hippocampe gauche avaient un déficit d'adaptation aux paroles et de la représentation intégrée des chansons. Puis, nous avons étudié l'organisation fonctionnelle de la mémoire des chansons dans une étude d'IRM fonctionnelle chez des volontaires sains (**étude 2**). Les résultats ont montré l'implication de l'hippocampe dans le processus de binding en mémoire des chansons ainsi que l'implication d'autres structures comme le gyrus frontal inférieur, les ganglions de la base et le cervelet. Enfin, dans une dernière étude (**étude 3**), nous avons examine la mémoire des chansons et plus particulièrement la mémoire de l'association (binding) des paroles au contexte musical chez des patients ayant bénéficié d'une résection unilatérale du lobe temporal médian pour traiter une épilepsie pharmacorésistante. La mémoire des paroles ainsi que celle du contexte mélodique des chansons a été testé dans une tâche explicite de reconnaissance. Un fort déficit en reconnaissance de paroles a été constaté chez les patients avec une lésion temporale gauche, et à un moindre degré chez les patients avec une lésion temporale droite. Ce déficit a été corrélé avec des déficits de la mémoire verbale. L'**étude 3** suggère, en outre, que les structures du lobe temporal médian peuvent être cruciales pour le codage de la liaison détaillée entre les paroles et leur contexte mélodique, tandis que les effets implicites d'une représentation intégrée de la chanson peuvent être épargnés après des lésions du lobe temporal médian. Pour conclure, ces trois études ont apporté de nouvelles données sur le rôle du lobe temporal médian dans le processus de binding dans le domaine musical. Ce travail a également permis d'identifier un vaste réseau de régions corticales et sous-corticales impliqué dans l'encodage de nouvelles chansons avant de discuter les implications théoriques et cliniques de ces recherches.

Mots-clé : chanson, mémoire, binding, épilepsie du lobe temporal, hippocampe

Abstract

Songs naturally couple music with language, constituting one of the most broadly used forms of music expression. Interestingly, songs require the simultaneous and integrated process of verbal (lyrics) and musical (melody) information to form a single memory trace. The medial temporal lobe has been identified as the key region for the integration of features of an event in episodic memory, also called the binding function. Nevertheless, the mechanisms by which the brain binds lyrics and melodies in song memory remain poorly understood. The purpose of this thesis is to elucidate the role of the MTL on the binding of lyrics and melodies for the creation of a unified song memory trace. First, the effects of unilateral hippocampus sclerosis on song processing were investigated in an fMR-adaptation study (**Study 1**). Patients with left hippocampal sclerosis showed adaptation deficits in response to lyrics as well as to the integrated representation of songs. To further explore the relation of these results with the emergence of memory for songs, the functional architecture of song memory was examined in a subsequent memory fMRI study (**Study 2**). The results support the implication of the hippocampus in song binding. Furthermore, the role of other structures, including the Inferior Frontal Gyrus (IFG), the Basal Ganglia (BG) and cerebellum was highlighted and discussed. Finally, **Study 2** was adapted to test binding in patients following a unilateral temporal lobe excision for the relief of intractable temporal lobe epilepsy behaviorally in **Study 3**. Memory for lyrics as well for their melodic context was tested in an explicit recognition task. A strong deficit in lyrics recognition was found in patients with a left temporal lesion, and to a smaller degree in patients with a right temporal lesion. This deficit was correlated with deficits in verbal memory. Evidence from **Study 3** further suggests that MTL structures may be crucial for encoding the detailed binding of lyrics with their melodic context, whereas implicit effects of an integrated representation of the song may be spared after MTL lesions. Altogether the studies presented in this thesis provide novel evidence for the role of the medial temporal lobe structures in binding lyrics and melodies for song memory. The present thesis proposes a comprehensive network of cortical and subcortical regions cooperating to successfully encode new songs. Finally, theoretical and clinical implications of these findings are considered.

Keywords: song, memory, binding, temporal lobe epilepsy, hippocampus.

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Para Flavio, por ponerle música y memoria a estos años… y por todo lo demás.

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Preface

The purpose of this thesis is to elucidate the role of the medial temporal lobe (MTL) on the binding of lyrics and melodies for the creation of a unified memory trace for songs. The integration of features of an event in memory, or binding, has been largely studied mainly within the visual domain, and is described to take place in the MTL. Nevertheless, less is known about the binding of higher-order auditory information such as songs. This thesis aims to provide an original account of the neural mechanisms underlying binding in songs taking a neuropsychological and neuroimaging approach.

The theoretical part will present the literature in which this thesis is grounded. First, *Chapter 1* introduces the concept of binding and the advances in cognitive neuroscience to understand this function in relation to memory. Then, *Chapter 2* reviews the literature in song processing. At the end of the theoretical part, *Chapter 3* will formulate and expose the key research questions addressed by this thesis.

The experimental part starts by introducing general methodological considerations (*Chapter 4)* on the experimental approach taken in this thesis, followed by three studies in the form of original research articles. In *Chapter 5*, the effects of unilateral hippocampus sclerosis in song processing are examined using an fMR-adaptation paradigm on the integration of lyrics and melodies in song perception (Study 1). Next, in *Chapter 6*, binding of lyrics and melodies for song encoding is investigated with a subsequent memory fMRI study in healthy controls (Study 2). Based on these findings, *Chapter 7* (Study 3) assesses the memory for lyrics and their melodic context in patients following a unilateral temporal lobe excision for the relief of intractable temporal lobe epilepsy.

Finally, the general discussion section (*Chapter 8)* summarizes novel findings of this thesis, and discusses their joint relevance and limitations in light of the current literature. Future directions for research and clinical implications are considered.

Theoretical part

Chapter 1: The binding function

Our daily experiences are often perceived and remembered as continuous events in space and time. Nevertheless, it is widely accepted that different sensory information of the objects within events are processed in disperse areas of the brain and during different time windows. Even features of an object from the same sensory modality may be processed in different regions of the cortex, for instance color, shape, and movement in the visual domain, or frequency, timbre, and duration in the auditory domain. Therefore, further processing may be needed to ensure the unified experience of objects and/or events as single units with particular feature configurations (i.e. a rose may have red petals and green leaves; a garden scene may contain several elements, such as roses and their smell, the sound of birds, flying bees, etc.) and as differentiated elements within a given environment (i.e. the rose is segregated from the bee flying around it, the sound comes from the birds and not from the tree, etc.), which involve binding mechanisms. This chapter introduces the definition of binding on which the following investigations are based, and provides background on the historical use of the term in neuroscience, and the neurocognitive bases of the binding function in humans.

a. Definition and general considerations on binding

The binding function refers to the cognitive ability to integrate multiple sensory features into a unified representation of a single object or event in perception and memory. From a philosophical standpoint, “the binding problem" refers both to the question of how the brain deciphers the elements composing a unified complex scene (i.e. colors and shapes of individual fruits in a bowl), and how it integrates the elements into a unique representation (i.e. fruit bowl composed by particular fruits). In the present thesis we will focus on the second characteristic, the integration of features (lyrics and melodies) into a unified object representation (song) and its encoding in memory. It is important to note that under this concept, binding may occur at two different levels: a perceptual level, acting on the representation of integrated percepts, and at a mnemonic or relational level, by encoding a stable version of the integrated representations. In the present thesis, we will use the term “integration” to refer to perceptual binding, and “binding” to refer to memory binding.

At a perceptual level, integration guarantees the correct association of features of an item into a unified percept (Holcombe, 2010; Robertson, 2003; Treisman, 1996). At a memory level, the association of different representations of items and their spatial and temporal context results in the encoding of a unique event (Davachi, 2006; Opitz, 2010; Roskies, 1999; Schlichting and Preston, 2015; von der Malsburg, 1981,1994). However, perceptual and memory binding boundaries in the empirical world may be blurred. If we take again the example of a fruit bowl in a still-life scene that contains a banana, two oranges, an apple, and a cluster of grapes, this image may be processed in such a way that each fruit represents an item that is later bound into a memory trace for the fruit bowl as a whole. On the other hand, the fruit bowl may also be represented as an item itself that needs to be bound into the still life scene (relative position on the table, background color, general shape), in which case the identity of the fruits may become irrelevant, with a different perceptual experience and resulting memory trace based on the same scene. Such phenomenological aspects of binding may rely on different brain mechanisms and shape the degree of vividness and detail with which experience and memories are perceived and encoded. To overcome the difficulty of the various levels of complexity that could be posed by the binding problem, a wide variety of experimental approaches in neuroscience have been used, from computational studies to animal lesion studies, and studies in humans applying neuroimaging and neuropsychology methods.

b. Binding in Cognitive Neuroscience: An historical perspective

Like many other functions in psychology, the study of binding arose from evidence of its failure. Cognitive psychologists studying visual integration of object features in perception discovered the existence of “illusory conjunctions” (Prinzmetal, 1981; Treisman and Gelade, 1980; Treisman and Schmidt, 1982). Illusory conjunctions are failures to integrate object features when the sensory and attention systems are overloaded or when stimuli are not given enough exposure. In a classic experiment, Treisman and Schmidt (1982) presented digits followed by three colored letters that subjects had to report later. When attentional resources were saturated by a digit task, a high proportion of illusory conjunctions occurred, in which participants reported seeing the letters with a wrong color and in different locations, suggesting an integration failure.

In 1996, Treisman formally exposed “the binding problem” and formulated the *Feature Integration Theory of Attention*. In this theory, she discussed three main possible solutions to account for the binding of object features in perception: 1) the existence of unique conjunction cortical neurons that only respond to the specific binding of features; 2) the synchronized firing of dispersed groups of neurons responding to the features of the object; and 3) an overlap in the spatial distribution and spatial attention of an object’s features. The first solution was that unique cells respond to unique object representations. This hypothesis was flawed very simply due to an economic principle. Too many neurons would be required to code for all the possible associations and bound representations that humans manipulate throughout their lives. Furthermore, the interference produced by overlapping features of other objects, as illustrated, for instance, by the stroop task (Stroop, 1935), rejects the possibility of a unique coding of such bindings (Barlow, 1972). The second solution for synchronized firing has been subsequently supported by a vast number of studies (for a review see Dan and Poo, 2006), in agreement with the famous quote that has illustrated the principles of Hebbian theory: “neurons that fire together wire together”. Nevertheless, synchronicity alone could not explain the simultaneous successful binding of several objects, or in other words, why the feature of an object is not confounded with the feature of another object if two objects are presented simultaneously. Thus, synchronized firing also requires a third solution, the allocation of spatial attention and the spatial distribution of features, upon which Treisman builds the *Feature Integration Theory of Attention*. This applies very well in particular for the visual cortex, which is spatially organized (Engel et al., 1997; Kass, 1997). In this way, several characteristics of an object, processed in different areas of the brain, can then be associated to a particular location and a specific timing for its unified perceptual representation.

However, the concept of binding and its role in memory was first introduced in cognitive neuroscience by computational studies (Cohen et al., 1997; Damasio, 1989; Fuster, 1997; McClelland et al., 1995; von der Malsburg, 1981). Already in 1989, Damasio hypothesized some required characteristics for a binding network. Sensory processing of features was described to happen at the sensory cortex in a dispersedly distributed and highly specialized manner. The binding object features would then require the spatio-temporal co-occurrence of stimulation, triggering the synchronized activation of those disperse areas, and furthermore eliciting phase-locking unification. He suggested that these areas would need to be interconnected with what he called "convergence zones". Such convergence zones were hypothesized to be in cortical and subcortical limbic areas, the basal ganglia and associative cortex. It was also speculated that these convergence zones would be differentially activated in relation to the degree of complexity and the modality of the information to be bound. Most importantly, "binding of conjunctions", or in our terms the encoding of integrated representations, would only be allowed through recursive feedback communication between convergence zones and the disperse activation of sensory cortex. It is surprising how this early theoretical framework already highlighted feedback and the continuous updating of information between neocortex and convergence zones, which were later identified as the medial temporal lobe (MTL) (Bast, 2007; Cowell et al., 2010; Eichenbaum, 2000; McClelland et al., 1995; Norman, 2010; O'Reilly et al., 2014; Rolls, 1996; Turk-Browne et al., 2006).

According to connectionist models, perceptual representations, along with the creation of new memories, depends on a large distributed network in the brain (for a review see Cer and O'Reilly, 2006). A particularly successful computational model that aimed to account for memory formation was the Complementary Learning Systems model (McClelland et al., 1995; for updated reviews of this model see Norman and O'Reilly, 2003; Norman, 2010; O'Reilly et al., 2014). The main original idea of this model was to propose two specialized learning and memory systems, which cooperate together to ensure successful learning and memory. On the one hand, one sparse system, dependent on the hippocampus, will be specialized in the initial encoding and rapid learning of episodic memories. This pattern-separated system, would avoid the interference of newly events with previous knowledge already acquired in the neocortical system. On the other hand, the neocortex would support a distributed system, where new memories will be gradually transferred and interleaved with knowledge structure represented by exemplars, or in other words, representing overlapping semantic structure of long term memories. Thus, memory consolidation would be accomplished by the recurrent communication between hippocampal and neocortical systems, producing the reactivation of previous knowledge, but also ensuring the reinstatement of exemplars that will update the knowledge structure. Note that the hippocampal system here allows encoding through pattern-separation and completion processes that ensure the binding of specific feature combinations into a unique representation.

The mechanistic ideas proposed by connectionist models in cognitive psychology were soon experimentally tested by animal studies, converging with the previous tradition of associative learning, and providing neuroanatomical evidence for the binding function in the medial temporal lobe (MTL) (Bussey and Saksida, 2005; Rudy and Sutherland, 1995; Sutherland and Rudy, 1989). Thanks to the development of neuroimaging techniques, more recent evidence from human studies has further supported the idea that memory encoding and consolidation strongly rely on hippocampal-neocortical networks (for a review see Wang and Morris, 2010). In sum, the investigation of the binding function emerges from the confluence of cognitive psychology and computational neuroscience from 1980 on, and remains an enduring research area. However, to understand the relevance of binding in memory models, a digression on the study of the medial temporal lobe (MTL) function in cognitive neuroscience needs to be made. The following section will present a perspective on MTL function and review evidence for the neurocognitive bases of binding.

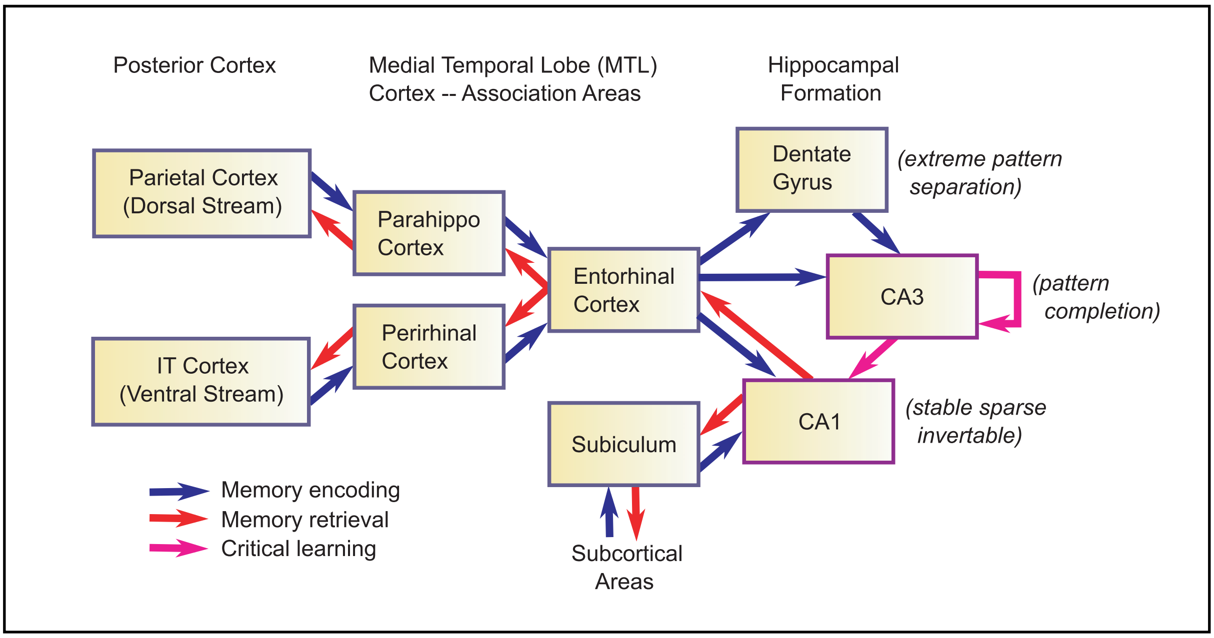

Figure 1. Hippocampal memory formation based on the Complementary Learning Systems model, showing how information is learnt (pink arrows), encoded (blue arrows) and retrieved (red arrows). (Source : O'Reilly et al., 2014)

c. MTL function and the neurocognitive bases of binding

The MTL is formed by various structures that are cytoarchitectonically different: the hippocampus and the surrounding cortex: the entorhinal, perirhinal and parahippocampal cortex (Amunts et al., 2005; Zola-Morgan and Squire, 1993). The early work by Brenda Milner and colleagues evaluating patients with lesions in these areas opened avenues for the investigation of the various aspects of memory that are differently represented and coded in the brain (Scoville and Milner, 1957; Milner et al., 1968; Milner et al., 1998). Today, the role of the MTL in episodic memory formation is undisputed. However, scientists still widely investigate the specific roles and relations within its substructures along the various phases of memory processes (i.e. encoding, consolidation, retrieval, reconsolidation, etc.) and subprocesses as familiarity, recollection and most importantly for the purpose of this thesis, binding.

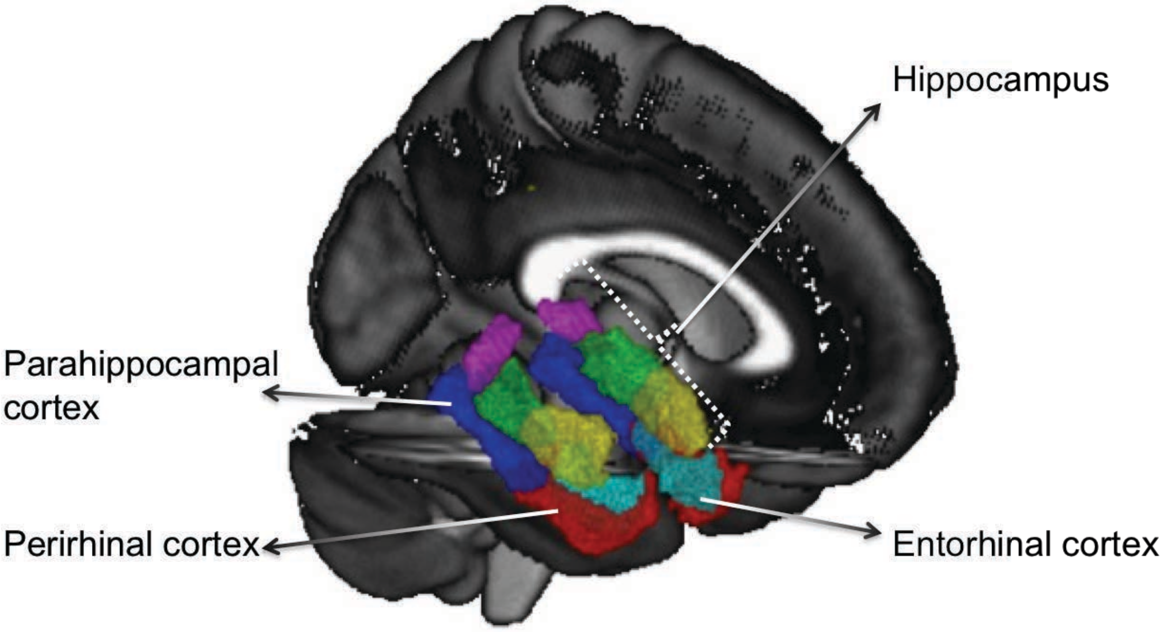

Figure 2. Medial temporal lobe structures : Hippocampus head (yellow), body (green) and tail (pink) ; entorhinal cortex (cyan); perirhinal cortex (red); parahippocampal cortex (blue).

For many years, a dominant view in memory recognition subdivided recognition in two qualitatively processes: familiarity and recollection (for a review see Eichenbaum et al., 2007; Montaldi and Mayers, 2010; Ranganath, 2010a, Yonelinas, 2002; Yonelinas, 2010). On the one hand, familiarity is a distributed process that follows the rules of signal detection targeting a sense of knowing or having had previously experienced something. On the other hand, recollection is defined as an all or nothing process that may be require the identification of details of an object or scene. Of note, recollection must be based on an integrated representation that binds all the details of an event together. Familiarity, recollection, and novelty processes, were then suggested to depend in different structures within the MTL (Daselaar et al., 2006).

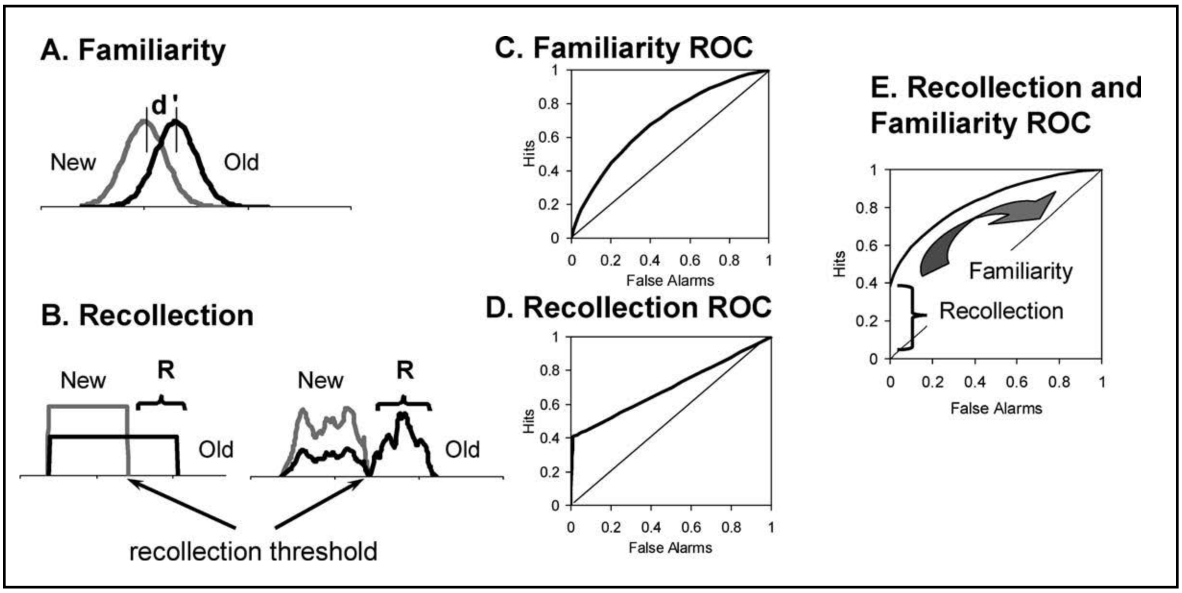

Figure 3. Illustration of the familiarity and recollection based on the Dual-process signal detection model. (Source : Yonelinas et al., 2010).

The empirical observation of familiarity and recollection was first neuropsychological, motivated by the assessment of patients with lesions in the MTL (Addante et al., 2012; Aggleton et al., 2005; Eichenbaum et al., 2007; Mandler, 1980; Yonelinas et al., 1998; Yonelinas et al., 2002). Most of the studied participants were patients with temporal lobe epilepsy assessed before or after surgical removal of unilateral anterior temporal lobe (see the methods section for more detail). Based on signal detection methods from psychophysics, the receiving operating curves were applied to examine recognition memory. Results show that while the hippocampus is engaged in encoding and binding details that lead to recollection, the surrounding perirhinal and parahippocampal cortex can support familiarity (for items and context respectively) with certain independence of the hippocampus (for a role of the hippocampus on both recollection and familiarity see Cipolotti and Bird, 2006; Kirwan et al., 2010; Wais et al., 2006; Wixted and Squire, 2011).

Nevertheless, the exclusively mnemonic function of the MTL has been challenged, and suggestions that it also plays an important role in perception have been made (for a review, see Baxter, 2009; Graham, Barense, and Lee, 2010; Suzuki, 2009). Although this idea was already presented by Jacoby and Dallas (1981), it was not until recent neuroimaging results that it has been incorporated into global accounts of MTL function. Activation in the perirhinal cortex has been associated with the recollection of item features and familiarity (Brown, 2008; Greve, Evans, Graham, and Wilding, 2011; Strange, Otten, Josephs, Rugg, and Dolan, 2002; Winters, 2004) but also for item identification (Lee et al., 2005; Murray and Richmond, 2001; Taylor, 2006).

Similarly, the hippocampus has also been suggested to be involved in complex discriminations (Barense et al., 2010) and implicit perceptual anticipation triggered by perceptual learning (Turk-Browne et al., 2010) among other perceptual tasks (Graham et al., 2006; Schapiro et al., 2012). These findings have led some authors to suggest that the perirhinal cortex and the anterior hippocampus are involved in high-level perceptual processing of objects. Supposedly, the former is engaged in object processing whereas the latter integrates different elements of scenes in order to create a bounded percept (Lee et al., 2006).

Based on neuroimaging and neuropsychological results, a comprehensive non-modular view of memory and perception, the Emergent Memory Account (EMA), has been developed by Graham et al. (2010). According to this model, memory arises from a dynamic interaction between the perceptual representations distributed through the whole brain. On the one hand the prefrontal cortex interacts within this cortical network adjusting performance according to task demands. On the other hand the MTL contributes to the instauration, consolidation/update and retrieval of the representations. Therefore, the same anatomically distributed network responds for both memory and perception with some structures being more or less important than others at different stages of the process.

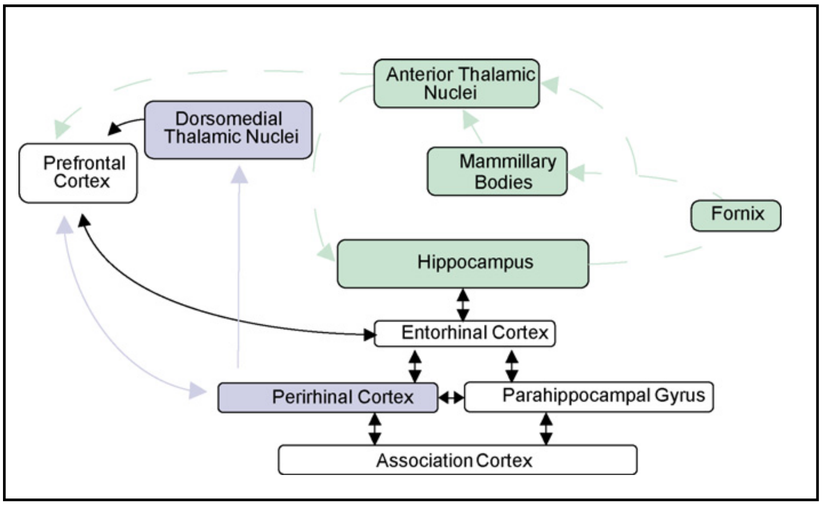

Figure 4. Long-term declarative memory network from Graham and colleagues (2010). The diagram show that MTL structures, may differentially support recollection (green boxes and arrows) and familiarity (purple boxes and arrows).

From this viewpoint, the role of the MTL is not restricted to long-term memory but also involves short-term and working memory (Axmacher et al., 2007; Lee and Rudebeck, 2010a; Rose et al., 2012; Zarahn, 2004) as well as perceptual processes (Lee, Bussey, et al., 2005; Lee, Buckley, et al., 2005; Lee, 2006; Lee and Rudebeck, 2010b). In other words, the EMA proposes a parsimonious hypothesis of brain functioning whereby memory emerges from a hierarchical organization of perception in a large brain network with a key role of the MTL and particularly of the hippocampus in the integration of complex information, or in other words, in perceptual and memory binding.

Building upon these studies, the growing interest on describing the particular elements that differentiate MTL structures' roles has led to a new approach considering binding as the core function performed by the MTL. Instead of building up on the psychological distinction between familiarity and recollection to examine the different processes that affect recognition, researchers have begun to focus on the kind of information that is processed, and more importantly, how this information is bound to form an event that will be different than the following one. Few attempts have been made to theorize binding while focusing on such interactive aspects of memory. Here, I will present two: the hierarchical Relational Binding Theory (hRBT) (Shimamura, 2010) and the Binding Item and Context (BIC) model (Davachi, 2006; Diana et al., 2007; Ranganath, 2010b).

Although both theories have placed the hippocampus at the top of the processing hierarchy, they differ in the articulation of binding in other MTL structures. The hRBT suggests that episodic events can be divided into sensory and cognitive units that could later be bound in the MTL. By this account, the role of the MTL is crucial for the integration of the different features of an event in both storage and retrieval. This model proposes a mixed model in which the MTL has a general mnemonic binding function, and at the same time keeps parts of the dual-process theories. All in all, it proposes a quantitative memory strength modulation of the engagement of MTL structures by which the hippocampus, situated in the top of the hierarchy, is responsible for stronger memories and the surrounding cortex for weaker memories.

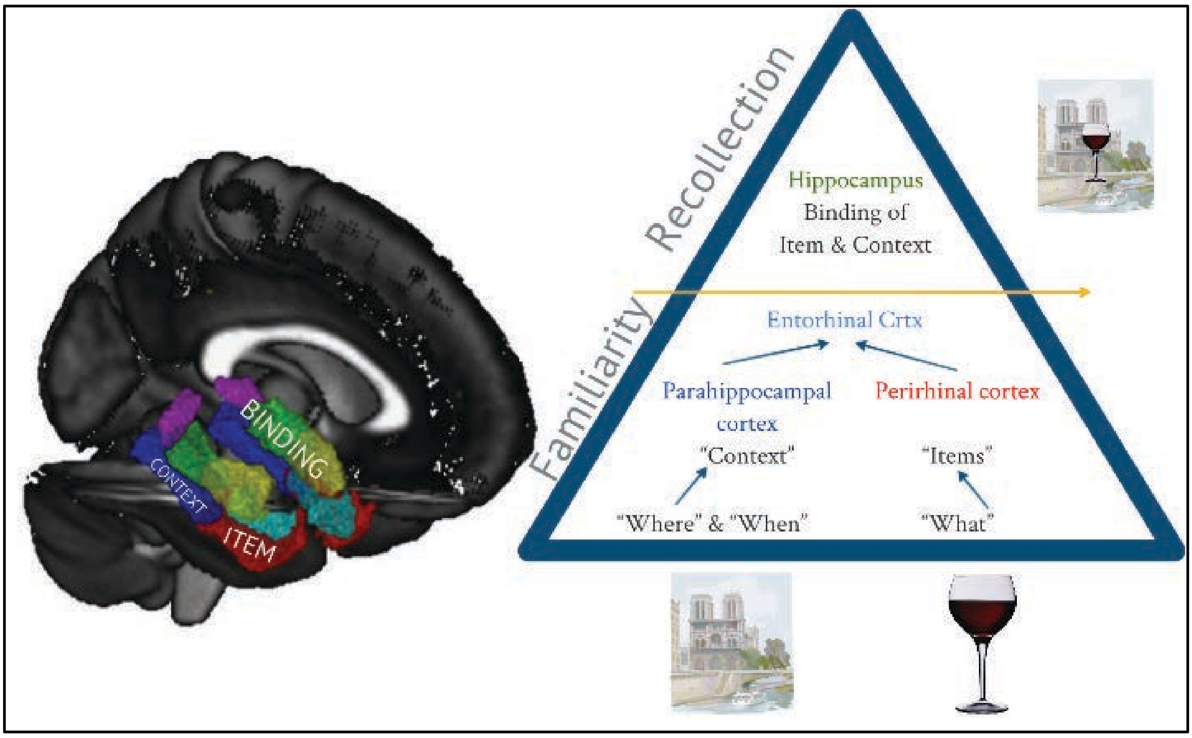

Figure 5. Diagram illustrating the BIC model adapted from Diana and colleagues (2007). When remembering to have drunk a glass of wine by the Seine in Paris, the Perirhinal would process the wine (its color, flavor, glass recipient, and other item characteristics), the parahippocampal would process that this happened by Notre Dame during your last holiday. Then, the hippocampus binds these pieces of information into a single event. Thus, in relation to the dual-process signal detection model previously discussed (Yonelinas, 1994), hippocampus will be in charge of recollection, whereas the surrounding cortex could signal familiarity to different types of information.

By contrast, based on neuropsychological and neuroimaging findings, the BIC model proposes a qualitative differentiation of MTL structures and a functional specialization that is dependent on the kind of information that is processed. This model stresses the importance of binding during both encoding (Davachi, 2006) and recollection (Diana et al., 2007). According to this model, the perirhinal cortex supports the encoding of items and item features (intra-item associations) (see Taylor et al., 2006 for cross-modal item associations), and is also described to play a role in certain complex perceptual tasks (Graham et al., 2010; Lee et al., 2006; Lee and Rudebeck, 2010b). On the other hand, the parahippocampal cortex supports the processing of the context in which items are presented. This context can include spatial (the *"where"*), temporal (the *"when"*) or even emotional information. According to the BIC model, all this is transmitted through the entorhinal cortex to the hippocampus, which is emphasized to be the key structure that binds items and context across time and space into a single memory trace (inter-item associations).

Thus, the perirhinal cortex is engaged in object processing and intra-item binding (e.g. of object colour and shape) (Buckley and Gaffan, 1998; Murray and Bussey, 1999; Buckley et al., 2001; Murray and Richmond, 2001; Bussey and Saksida, 2002; Bussey et al., 2005), whereas the hippocampus appears to be required to form conjunctive representations that bind several features across space or time (Barense et al., 2007; Barense et al., 2010; Bussey and Saksida, 2005; Cowell et al., 2006; Cowell et al., 2010; Diana et al., 2007; Eichenbaum et al., 1994; O'Reilly and Rudy, 2001; Winters, 2004). From this viewpoint, the selective recollection impairments observed in patients with hippocampal damage (Aggleton et al., 2005; Aggleton et al., 2006; Bowles et al., 2011; Incisa et al., 2004; Lancelot et al., 2005), or Alzheimer's Disease (Goll et al., 2011; Parra et al., 2009) could be interpreted as a compromised binding function, which is also in line with the perceptual deficits found in these patients (Chun and Phelps, 1999; Lee et al., 2006; Lee et al., 2005). The notion of binding across time both from perceptual (Engel and Singer, 2001; Joliot et al., 1994; Lin et al., 2006) and memory perspectives (Tubridy and Davachi, 2011; Dubrow and Davachi, 2014) is particularly relevant here, since auditory information, as opposed to visual information, is strongly tied to temporal processing, where information that unfolds over time contains the identity of the auditory object (see Jones, 1976).

Different materials have been used in binding tasks, including the binding of objects/shapes with their color, objects and scenes, objects/shapes with locations, and faces with names. However, few studies have incorporated auditory material for the study of binding.

d. Binding of auditory information

Binding of auditory information, or the unification of an auditory object or scene, can be exemplified by classic cocktail party psychoacoustic problem (Cherry, 1953). In the noisy environment of a cocktail party, we are still able to focus on a conversation, filtering out most of the other sounds that are irrelevant to the current interaction and distinguishing our interlocutor voice among the others. In other words, the cocktail party psychoacoustic problem highlights the human ability to attend to a specific sound or voice that is merged in a noisy context, integrating the several auditory features (see also Teki et al., 2011a) that conform, for instance, voice identity and the verbal message. Following this idea, the encoding of new songs may require, at least, the binding of lyrics with their melodic context.

The binding mechanisms described in the previous section are conceptualized to be modality general. However, the way that time and space relate to vision and audition may be a source of variation in terms of the network that interacts with the MTL. Despite the fact that binding is required to integrate spatial and temporal information, the latter has been seldom explored due to the modality bias in favor of visual studies (for studies on binding with auditory information see Dowling and Tillmann, 2014; Lancelot et al., 2005; Maybery et al., 2009; Overath et al., 2007; Overath et al., 2008; Sanders et al., 2011; Zhuo and Yu, 2011). Whilst vision requires a rapid binding of synchronous events (Engel et al., 1997) in order to ensure the coding of spatial properties, audition is more susceptible to time variations (Demany et al., 2010; Kiebel et al., 2008; Sanders et al., 2011) and may require the ongoing binding of sequences and the regulation of expectation. Therefore, it is plausible that other structures involved in sequence learning and temporal regularities detection, such as the cerebellum and the basal ganglia (Bostan et al., 2013; Kotz and Schwartze, 2010; Penhune et al., 1998; Schwartze et al., 2012), may play a role in auditory binding by enhancing learning of related sequences and temporal coupling.

In consonance with this hypothesis, sensori-motor perceptual binding has been shown to occur in the striatal system (Brown and Marsden, 1998; Graybiel et al., 1994). For instance, using a sonification experiment of a human avatar’s breaststroke, Schmitz and colleagues (2013) have shown a role for the basal ganglia in auditory-motor binding within a network that included the superior temporal sulcus, the insula and the right prefrontal cortex.

d. Binding of auditory information

Based on the role of the inferior parietal lobule (IPL) in auditory expectancy and feedforward connections (Rauschecker, 2013), this structure can additionally support auditory binding by sending feed-forward information that matches predictions with sensory output. This region has also been shown to be involved in visual feature binding (Shafritz et al., 2002). Different lines of evidence support the involvement of inferior parietal regions in the binding of auditory information, particularly when mental imagery is required (Zvyagintsev et al., 2013). For instance, areas located at the parieto-temporal boundary have been found to be active for audio-motor integration during mental imagery, as for instance during covert rehearsal or humming of auditory stimuli (Buchsbaum et al., 2005, 2011; Foster and Zatorre, 2010; Foster et al., 2013; Hickok et al., 2003). The angular gyrus has also been related to mental imagery (Herholz et al., 2012), calculation, speech processing, auditory short-term memory and perceptual binding (Albert et al., 2013; Kamke et al., 2012; Seghier, 2013).

Binding involving auditory information within and between modality may be illustrated by different situations. For instance, the unified representation of faces and voices (Campanella and Belin, 2007), locations of different sounds (Maybery et al., 2009), moving objects and their sound (Bushara et al., 2003; Schmitz et al., 2013), or the illusory conjunction produced by ventriloquism (Bischoff et al., 2007). The present thesis will exclusively focus on the binding of verbal and musical information, and more specifically in the case of encoding new songs.

Chapter 2: Song processing

Songs represent one of the most enjoyable and widespread forms of communication, emotion and cultural expression. From lullabies to requiems, our life is paced to the beat of our particular soundtrack. Although music and language may be considered two distinct sound systems, they become intimately entangled for songs such that when reading "imaging all the people" we can instantly imagine the words as they were sung by John Lennon. Songs require the simultaneous and integrated combination of verbal (lyrics) and musical (melody) components to form a single unit. Singing requires similar production mechanisms to speech, such as fine motor control of the vocal chords and larynges, but do we perceive songs as language, as music or as something else? In this section the different elementary psychoacoustic characteristics of music will be presented, followed by the particular interaction of language and music in songs. Then, evidence for the creation of an integrated representation of lyrics and melodies in songs will be reviewed. Behavioral and neuroimaging studies of song perception and memory will be considered to ground the study of binding in songs.

a. Music as a complex auditory stimulus

Music is a highly organized acoustic signal formed from sequences of sounds that unfold over time and that ultimately have particular aesthetic and/or cultural value within a given society. Although the necessity of music is still under debate, it is suggested that music could have been present at the dawn of human societies and it seems to be very intimately related to the origins of language (McDermott and Hausser, 2005; Mithen, 2005; Patel, 2008).

From an acoustical perspective, and as any other sound, music is characterized by the following elementary characteristics: pitch, timbre, duration, (rhythm, meter, beat, tempo, articulation) and loudness (dynamics). Additionally, in a second level of complexity, music is also constituted by harmony (tonality) and form (musical texture). The combined perception of the described elements and their unification into an auditory object, namely a piece of music, requires the activation of disperse areas in the brain that will be now briefly described.

Pitch is the perception of frequency and is processed in the primary auditory cortex. This area has a tonotopical organization, which means that the frequency range is reflected in the structure: low frequencies stimulate the anterior areas of the primary auditory cortex, and gradually, higher frequencies stimulate more posterior areas (Elberling et al., 1982; Lauter et al., 1985; Pantev et al., 1988, 1995) However, the ability to identify frequencies without any other sound reference, namely absolute pitch, is generally lost very early on in life and is only preserved in some early trained musicians (Baeck, 2002; McDermott and Oxenham, 2008). Instead, human intonation and melody discrimination relies more on the relations between pitch sequences, or, in other words, on relative pitch. The ability to identify melodies based on their relative pitch sequences (a sort of implicit transposition), unlike absolute pitch identification (Bendor and Wang, 2005), seems to be a privilege that is mainly present in humans as compared to other animals (Brosch and Scheich, 2002; D’Amato, 1988; Hulse et al., 1984). Consequently, a higher level of unification for the creation of a melody representation, irrespective of its absolute frequencies, needs to occur after the initial auditory processing. Such processing may be in part related to working memory and frontal functions. The inferior frontal gyrus (IFG), anterior cingulate cortex (ACC), inferior parietal lobule (IPL) and right superior temporal sulcus (rSTS) have been described to be involved in relative pitch processing. However, mesolimbic regions involved in sequence learning, such as the hippocampus or the striatum may be important to create a stable representation.

Duration refers to the length of sounds (notes), musical sentences and or musical pieces. Although it might seem a very simple concept, it is indeed one of the most complex dimensions in the understanding of music. As compared to other sensory modalities, time is inherently part of the identity of sound, and therefore timing and duration are crucially relevant to music cognition. Duration can be subdivided into beat, meter and rhythm (Peretz and Coltheart, 2003). Beat refers to a broad constant of “speed”, the underlying isochronous pulse to which the sounds unfold. This is in part overlapping with what is generally called tempo. On the other hand, meter refers to the organized accentuation of beat, creating a temporal context in which rhythmic patterns may be circumscribed. For a long time, research focused on melody and disregarded rhythmic processing, but the interest in understanding this musical aspect has recently increased (Cason and Schön, 2012; Gordon et al., 2011; Hove et al., 2014; Jerde et al., 2011; Magne et al., 2004; Overy and Turner, 2009; Patel and Iversen, 2014; Schulkind, 1999; Thaut, 2003; Thaut et al., 2008; Zatorre et al., 2007).

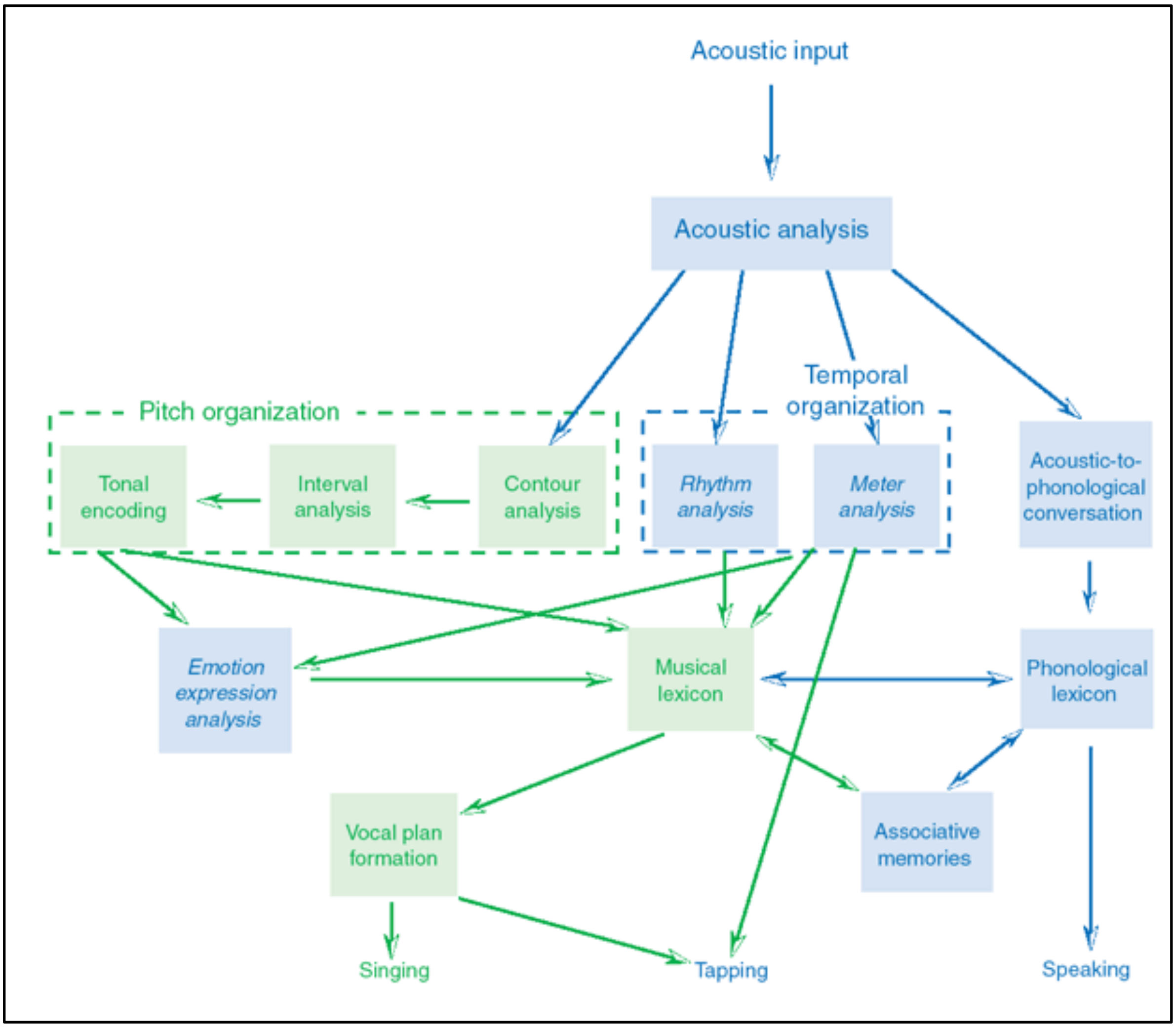

Figure 6. A modular model of music processing from Peretz and Coltheart (2003), as illustrated by Ivelisse Robles. Boxes represent processing components and arrows represent pathways of information flow between them. Components specific to the music domain are shown in green and those specific or shared with language in blue.

Interestingly, it has been suggested that a strong motor component is attached to the mental representation of music rhythm. This is typically illustrated by the activation of premotor cortex, supplementary motor area (SMA), and other regions such as the cerebellum and basal ganglia, which are involved not only in the production but also the perception of rhythm (Thaut et al., 2008). Rhythm has been frequently reported to be left lateralized in the superior temporal gyrus (STG). This could be related to the more abstract and analytic nature of the rhythmic function and the sequencing of stimuli. A number of studies speak for a relationship between rhythmic processing and timing and sequencing, suggesting the involvement of structures such as the insula, basal ganglia and cerebellum (Grahn and Watson, 2013; Schwartze et al., 2012; Thaut, 2003).

Timbre is a sensory characteristic determined by the degree of complexity of the vibration of a body. Right hemisphere dominance has been described for the timbre processing that engages primary and secondary auditory cortex (Baeck, 2002; Halpern et al., 2004; Platel et al., 1997; Samson and Zatorre, 1994; Samson et al., 2002).

Harmony is traditionally perceived through the secondary auditory cortex, and can be defined as the vertical organization of intervals and the structural rules leading to harmonic progressions. In other words, harmony constitutes the skeleton of a musical piece, or, using linguistic terms, the musical syntax. Overlapping networks have been found for both harmony and syntax (Koelsch et al., 2005; Koelsch, 2011; Koelsch and Friederici, 2003; Koelsch and Siebel, 2005; Patel, 2003; Sammler et al., 2009; Sammler et al., 2009a). Patel (2003) framed these findings in the Shared Syntactic Integration Resource Hypothesis, which suggests an overlap in the neural mechanisms that provide the resources for syntactic integration, with independence of domain. Harmony is perceived regardless of formal knowledge of musical structure. Similarly to language, and regardless of expertise, statistical learning and implicit exposure govern the acquisition of harmony rules (Jonaitis and Saffran, 2009; Pearce et al., 2010). Activation in Broca's and Wernicke's areas have been systematically reported bilaterally in response to harmony (Patel, 2003; Koelsch, 2006), a finding that suggest an overlap of language and music processing. Nonetheless, harmony processing has a bilateral pattern as opposed to the extremely left lateralization of linguistic syntax. Harmonic knowledge also engages activation of other structures specific to music such as the STG (Patel, 2003; Sammler et al., 2009). Moreover, harmony processing is crucial for the perception of consonance/dissonance, and is indeed biased by learning and enculturation (McDermott and Oxenham, 2008), therefore having an impact on emotional and aesthetic judgments that go beyond structure itself (Omigie et al., in press).

It is worth mentioning that besides the described formal characteristics of music, there is another inherent component of great relevance: emotion. To this end, subcortical nucleus of the limbic and the paralimbic system are also recruited during music perception. The particular involvement of emotion in music memory will not be reviewed in the present thesis. Nevertheless, a tangential scientific work discussing this issue in the context of the present studies can be found in Annex A (Alonso et al., 2015).

b. Music and language integration in songs.

Both music and language can be considered communicational codes (Hachinski and Hachinski, 1994). They both are based in organized sounds, with their identity depending on, among other things, rhythm, melodic contour and a hierarchical structure. In the last three decades, much research has been conducted to delimit the independent and shared neural resources used by these two domains (for a review see Patel, 2008). For instance, asymmetries in the auditory cortex have shown that left auditory cortical areas have better processing temporal resolution, required for the rapidly changing broadband speech sounds, whereas right auditory cortical areas are better in spectral resolution, more relevant to frequency accuracy (Zatorre and Belin, 2001) that is required for melodic processing. Furthermore, certain domain independence has been supported by double dissociations in aphasics and amusic patients, whereby deficits are shown in one domain but not the other (i.e. Hébert et al., 2003; Tzortis et al., 2000). However, to date, it is widely accepted that, despite asymmetries in the auditory cortex function for processing low-level features (i.e. accurate fine-grained representation of pitch, Zatorre and Baum, 2012; Zatorre and Belin, 2001), music and language processing share abstract high-level neural mechanisms.

Beyond the inherent theoretical interest of using music as a tool to reveal the general nature of brain cognitive functions, one motivation for the research in this field has risen from the idea of transfer of training between music and language domains (Besson et al., 2011; Kraus and Chandrasekaran, 2010; Ludke et al., 2014; Moreno et al., 2011; Schön et al., 2008). For instance, it has been suggested that musical training can benefit pitch contour discrimination in both music and speech perception (Schön et al., 2004), implicit learning of musical and linguistic structures (Francois and Schön, 2011; Selchenkova et al., 2014), and verbal memory (Chan et al., 1998; Ho et al., 2003). Particularly, music and speech perception seem to be similarly influenced by rhythmic cues (Hausen et al., 2013). Rhythmic training has been shown to improve phonological processing (Cason and Schön, 2012) and also to enhance phonological production in hearing-impaired children (Cason et al., 2015a). Moreover, songs, as compared to speech, facilitate children’s phonetic recognition (Lebedeva and Khul, 2010), and audio-motor training compared to auditory training alone has been shown to enhance phonological perception of sentences (Cason et al., 2015b).

Similarly, from a perceptual viewpoint, phonemic information has shown to facilitate melody and speech imitation, suggesting shared resources for musical and verbal vocal production (Mantell and Pfordresher, 2013). This idea of transfer has also gained interest in clinical fields, suggesting a potential application of music in cognitive rehabilitation following brain damage based on the training of alternative compensatory pathways that may allow access to common functions (Baur et al., 2000; Moussard et al., 2012; Patel, 2011; Simmons-Stern et al., 2010; Thaut et al., 2008).

Indeed, music and language can be written, read, listened to or vocally expressed through speaking and singing. To this end, songs represent an ecologically valid and particularly relevant stimuli because they require the simultaneous and integrated process of verbal (lyrics) and musical (melody) components to form a single unit. Furthermore, singing is a widespread behavior that requires similar production mechanisms as speech for fine motor control of the vocal chords and the larynges.

A comprehensive description of brain areas involved in singing has been elucidated using neuroimaging methods such as PET (Brown et al., 2004; Perry et al., 1999) and fMRI (Koelsch et al., 2009; Riecker et al., 2000; Zarate and Zatorre, 2008). The singing network engages primary and secondary auditory areas, corresponding to Helsch's gyrus and the STG, together with other areas involved in vocalization and audio-motor integration. These motor activations include the mouth region of the primary motor cortex, the SMA, which is involved in the planning and execution of speech, the frontal operculum and the anterior insula, both of which cooperate for articulatory processing, and finally basal ganglia (in the left putamen and right palidum) and (posterior) cerebellum activations which are related to timing, sequencing and fine audio-motor coordination (Brown et al., 2004; Perry et al., 1999).

A remarkable overlap in the storage and rehearsal of verbal and tonal acoustic information has being reported in the frontal operculum (Koelsch et al., 2009), which suggests that this structure carries out an essential role in the representation of the larynx and the pharynx in sound production control. This is in line with the speech suppression found in patients with bilateral damage of the frontal operculum (Villa and Caltagirone, 1984). Similarly, the activation of anterior insula has being related to overt articulatory processing in speech and singing, with left-lateralized activity for the former and right-lateralized activity for the latter (Ackermann and Riecker, 2004; Riecker et al., 2000; Zarate and Zatorre, 2008).

This lateralization pattern has also been reported for the SMA and cerebellum (Riecker et al., 2000).

Interestingly, a particular role of the temporal poles has been described in relation to higher-level music tasks, including harmonic processing, which has led some scientists to label it as a tertiary auditory cortex (Brown, 2004). Conversely, the role of the temporal poles in language has rather been linked to sentential semantic processing and object naming (Tsapkini et al., 2011), which suggests that its role in harmonization may be particular to singing. However, evidence from a lesion study rather highlights the role of the right temporal pole in musical identity processing (Hsieh et al., 2011). A more general view on the temporal poles has related them to the processing of high-level perceptual features of stimuli that integrate multisensory information and emotions (Olson et al., 2007). This finding suggests that the role of the temporal poles in singing could also be related to high-level processing of melody identity and emotion, rather than particular harmonic or musical syntactic features. Furthermore, other studies focusing on harmonic processing, understood as musical syntax, have instead systematically underlined the involvement of other structures such as the frontal operculum, which is more coherent with the syntax processing role of these two structures in language (Patel, 2003; Sammler et al., 2011; Tillmann et al., 2006).

Although the study of singing production lays out the scope of the present work, which will henceforth focus on song perception and memory, this brief background on the substrates of song production is important to understand our object of study: the unified representation of a song and the creation of its memory trace.

i. Song perception

Containing verbal and musical information, are songs perceived and stored as language or as music? Are they musical language, verbal music, or a gestalt that is more than simply the sum of text and melody?

All in all, the literature suggests a verbal dominance in the processing of songs, but also shows the involvement of additional regions that may be particularly activated for song perception compared to instrumental music or speech alone. The perceptual transformation of speech into song, for instance, implies a higher degree of pitch mapping and audio-motor integration related to rhythmic processing (Tierney et al., 2012). Such idiosyncrasies of songs may be partially responsible for the popularity of sung music, and the enhanced memory for vocal melodies over instrumental ones (Weiss et al., 2012).

Neuroimaging methods, and particularly fMRI, have greatly contributed to the exploration of the cerebral substrate that underlies song perception. Initial evidence from electroencephalography has suggested that there are independent signatures for melodic and semantic processing of songs (Besson et al., 1998). For instance, semantic incongruities in song perception have been associated with a greater amplitude N400 component, which is also reported in speech, whereas melodic incongruities during song perception have tended to trigger a greater amplitude P300 component, that has also been reported in instrumental music (Besson and Faïta, 1995). This independence of semantic and melodic processing of incongruities has also been supported behaviorally by divided attention studies using a dual-task paradigm (Bonnel et al., 2001). Furthermore, the detection of deviants in familiar songs has revealed laterality differences related to material in magnetoencephalography. Lyric deviants elicited a left-dominant M140, whereas melody deviants triggered right-dominant M130 response, supporting an independent processing of lyrics and melody information (Yasui et al., 2009).

However, it is important to consider that the semantic and harmonic incongruities compared in these studies may not be correlates of equivalent processes in music and language, as melodic incongruities refer to harmonic rules, which are more comparable to syntactic processing. Indeed, syntactic violations have been compared to melodic and harmonic violations, whereby similar greater P300 components have been reported for both processes (Besson and Schön, 2003), which suggests a common processing mechanism. Furthermore, syntactic violations in both music and language have been found to elicit an early negative component at 200 ms in the IFG and anterior STG (Sammler et al., 2009). In line with this result, patients with lesions in Broca’s area have also shown an abnormal scalp distribution of the early right anterior negativity (ERAN) in response to harmonic violations, which suggests that this structure has a domain-general role in processing syntactic information (Sammler et al., 2011). Using sung words in a same-different task, Gordon and colleagues (2010) found not only a larger N400 component for different words, but also a larger N400 (that was followed by a positive component) for different melodies. In contrast to Besson and colleagues (1998), these findings suggest shared neural resources for semantic aspects of language and harmonic aspects of music.

b. Music and language integration in songs.

Of particular relevance to the present thesis are those studies that have investigated how the verbal and the melodic components of songs form an integrated representation and are ultimately bound. Using fMRI, two main methods of analysis have been employed to address this issue.

The first method uses the hierarchy subtraction logic, and assumes that contrasting songs (both lyrics and melodies combined) against the melody component alone allows visualization of the areas involved in the processing of the verbal component, while similarly contrasting songs against the lyrical component alone may reveal the areas involved in the processing of the melodic component. Adopting this logic in an fMRI study, Schön et al. (2010, Exp. 1) presented pairs of sung, vocalized melodies (defined as singing without words) and spoken words in a same-different task. The results revealed a common network including STG, Medial Temporal Gyri (MTG) and IFG bilaterally for the processing of both types of stimuli, suggesting overlapping cerebral substrates for the processing of lyrics and melodies.

Similarly, Merrill and colleagues (2012) decomposed and compared functional activations evoked by the verbal (i.e. words) and tonal components (i.e. pitch patterns) of song, and once again, revealed a shared network for both components in the STG and the precentral gyri bilaterally. Subtle lateralization differences were found in the IFG, with the verbal component of song being more lateralized to the left, and the pitch component to the right. Although such findings allow us to identify the cerebral network underlying the processing of lyrics and melodies, they do not elucidate whether lyrics and melodies are integrated or processed independently in song perception.

The second method to investigate the relationship between lyrics and melodies in song perception involves the repetition/variation of tonal-verbal components in songs. It goes a step further than the previous method by studying the interaction between the two components, and considers, therefore, that song perception is more than simply the sum of lyrics and melodies and additionally results in a bounded percept. In other words, this method suggests that one single auditory object will emerge from the perceptual binding of lyrics and melodies, which is different from the two components taken in isolation (for a review on binding see Opitz, 2010). This method examines brain activity modulations during repetition (same) or variation (different) of songs' components in order to investigate how they interact. Schön and colleagues (2010, Exp. 2) examined sung pairs of words that could vary or repeat in terms of the verbal and/or the melody component in a same-different task, and revealed an interactive processing of both verbal and musical components of the song material in the left and the right STG. In another study, Sammler and colleagues (2010) took advantage of an fMRI-adaptation paradigm in order to explore the cortical networks underlying the integration and the independence of lyrics and melodies in song perception.

In Sammler and colleagues' (2010) study, songs were presented to healthy participants in blocks in which the repetition of lyrics and/or melodies were varied in a factorial design. Results showed a bilateral involvement of the STG and STS for both components, consistent with Schön and colleagues (2010 Exp.1) and Merrill and colleagues (2012). Furthermore, a stronger adaptation to lyrics than to melodies was obtained in the left anterior STG/STS, which suggests that the processing of lyrics is independent of the processing of melodies in these areas. Interestingly, no brain area showed stronger adaptation to melodies than to lyrics. These data illustrate a putative asymmetrical relationship between song elements in that melodies are more tightly bound to songs than lyrics, which suggest that adaptation effects are strongly driven by the lyrics, at least in this paradigm. This study also demonstrates an integrated central processing of songs that takes place in the left mid-STS and the left premotor cortex. Specifically, at the level of the temporal lobe, a strong integration between lyrics and melodies was found in the left mid-STS whereas independent processing of lyrics was shown to depend on more anterior regions of the left STG.

Interestingly, these effects were interpreted in terms of a “gradient of integration” situated along the left STS following the functional (Binder, 2000; Davis and Johnsrude, 2003; Liebenthal et al., 2005; Scott and Johnsrude, 2003) and temporal (Kiebel et al., 2008; Overath et al., 2008; Patterson et al., 2002) hierarchy of auditory perception in the superior temporal lobe (Gow, 2012). Notably, this gradient, which was measured using the same integration contrast with more permissive thresholds, transformed the question of “whether” lyrics and melodies are integrated into the question of “the degree to which” they are integrated or independently processed in different cortical regions. In this way, the integration process is conceptualized dimensionally rather than categorically.

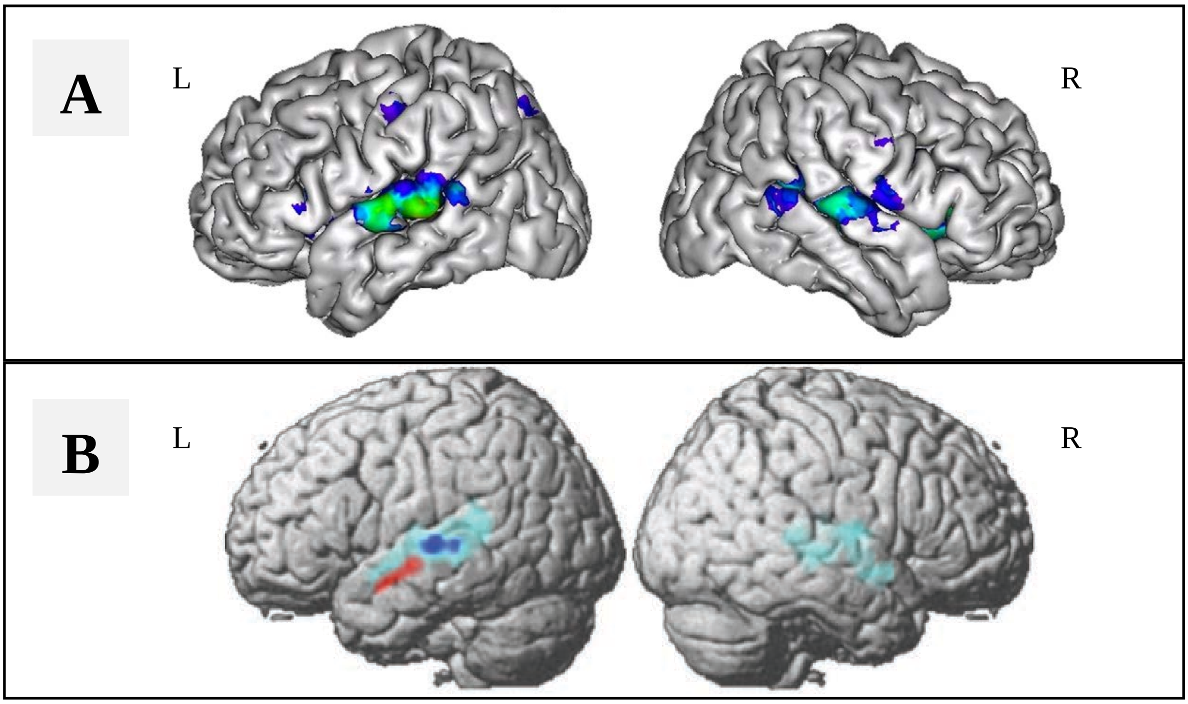

Figure 7. Areas of lyrics and melody interaction during song perception as reported by Schön and colleagues (2010), *p* < 0.05 corrected for multiple comparisons (A) and Sammler and colleagues (2010) showing strong interaction in blue (*p* < 0.001 uncorrected), weak interaction (*p* < 0.05 uncorrected) and no interaction in red (*p* < 0.001 uncorrected) (B).

Taking Schön and colleagues' (2010) and Sammler and colleagues' (2010) results together, the integrated representation of lyrics and melodies may be processed within the posterior part of the STG/STS in healthy participants. Nonetheless, the formation of memory traces that bind these lyrics and melody has not been addressed. Studying songs and the way they might become a unified percept provides a novel approach in investigating complex stimuli that integrate two different kinds of information. This sort of unified representation trace refers to binding, as it has been previously discussed in this introduction, and should be theoretically supported by the MTL function.

ii. Song memory

Studies with healthy population

The study of song memory has being approached from several angles. For example, researchers have delved into the autobiographical properties of songs memory (Bartlett and

Snelus, 1980; Janata et al., 2007), the influence of emotions (Ali and Peynircioglu, 2006; Schulkind et al., 1999), the influence of extra-musical information in its storage and retrieval (Halpern, 1984; Sherman and Kennerly, 2014), and, most relevant to the interest of the current thesis, on the differential encoding and integration of song components themselves and the cerebral substrate of memory for songs.

Pioneering behavioral work (Crowder et al., 1990; Serafine et al., 1984, 1986) addressed for the first time the issue of verbal and musical integration in relation to memory. These authors set up a series of experiments in which a list of songs had to be memorized and then recognized among other songs that were manipulated in different ways. In the first study (Serafine et al., 1984), songs in the recognition test were either exactly the same as those in the study phase (*original songs*), new songs with new lyrics and new melodies, songs with old lyrics but new melodies, songs with old melodies but new lyrics, or songs with old melodies combined with old lyrics of a different song (*mismatch* or *rearranged songs*). Their results showed that lyrics and melodies were better recognized when they were tested in the original song context in which they were presented than when tested in rearranged songs. Importantly, the familiarity associated to both elements was identical in the original and rearranged songs, which argues in favor of a memory advantage of an integrated song representation. Furthermore, melodies were shown to be near chance unless presented with the original lyrics, which indicates that melody recognition depended on lyrics more than lyric recognition depends on melodies.

These results have been found to remain consistent even when songs from the recognition test were sung by a singer different to that in the study phase, and also when participants were asked to make an explicit effort to retain the melody (Serafine et al., 1984, Exp. 2). Similar results have been yielded in later experiments with nonsense words, which indicates that semantic connotations are not responsible for this lyric-melody integration (Serafine et al., 1986, Exp. 1). Based on this result, the authors formulate an alternative interpretation of a superior memory for an integrated representation, namely, that a decrement in memory for melody and words presented in the rearranged condition could be caused by the distracting wrong context. However, melodies were equally recognized in the rearranged condition and when presented without words (hummed melodies), refuting the decrement hypothesis. Furthermore melodies were better recognized in the *original* song than when presented without words, arguing in favor of a superior memory for an integrated representation (Serafine et al., 1986, Exp. 2). The same results were found for lyrics recognition (Serafine et al., 1986, Exp. 3). Altogether, these experiments have provided strong evidence for an integration effect, a tendency for lyrics and melodies to be better recognized when presented in the original melody or lyric context respectively.

To examine a variety of explanations for this integration effect, Crowder et al. (1990) tested two different hypotheses. First, the "*physical interaction hypothesis*" posits that one element exerts subtle physical changes in the other, making its representation more distinctive than if it were presented with a different combination. To test this, they used songs with nonsense words and phonological deviants of these words to explore whether melody recognition is improved by the phonological similarity of the lyrics with which the melody has being studied, or in different words by submelodical information added to the memory trace. Their results support this hypothesis; melodies within *original songs* were better recognized than *rearranged songs*, even when using nonsense words and their phonological deviants.

Second, the "*association by contiguity hypothesis*" proposes that the co-occurrence of stimuli build up an association, which may be responsible for the memory benefit in spite of an integrated representation. To this end, they presented hummed melodies simultaneously with spoken texts and compared their memorability when in a recognition test with songs and a recognition test with hummed melodies with spoken texts. Melody recognition was superior for original than for mismatch songs regardless of recognition test type, suggesting that the joint storage of elements, forming paired associates, can facilitate encoding. However, it is difficult to rule out the fact that participants may have created song-like integrated representations from the presented material. The authors underline the influence of temporal contiguity on encoding, examining the co-occurrence of various factors that may support the reported integration effect. In sum, these results suggested that integration could be attributed to an integrated representation (Crowder et al., 1990, Exp. 1 and 2), but also to associations between independent elements (Crowder et al., 1990, Exp. 3).

Utilizing a different approach based on the idea of divided attention (also see Bonnel et al., 2001), Racette and Peretz (2007) investigated the effects of learning unfamiliar lyrics by singing them, speaking them or in a divided condition in which lyrics were spoken but accompanied by music. In contrast with the integrative view of memory for songs, their results showed lyrics and melodies to have a different representation in memory, which leads to impairment in the dual task (learning the lyrics and the melodies together by singing). The authors suggests, perhaps counterintuitively, that one should not sing when wanting to learn lyrics of new songs. However, this may also imply that a second level of processing – binding – may be required for the emergence of an integrated memory trace of the song when the elements are presented separately (spoken lyrics with accompanied music). This integrated representation could then be used for recognition.

Priming paradigms present another exploited way of investigating song memory. Research has demonstrated bidirectional and automatic cuing effects of lyrics over melodies and vice versa in familiar songs (Johnson and Halpern, 2012; Peretz et al., 2004a; Peynircioglu et al., 2008). In particular, Peretz and colleagues (2004a) argue against the temporal contiguity hypothesis, since reversed prime-target sequences were still able to result in an enhanced recognition. Peynirciogly and colleagues (2008) further explored this effect by looking at asymmetries between memory for lyrics and melodies that could weight their contribution to the final integrated memory trace. In their study, cueing effects of lyrics, melodies and titles of songs amongst one other were investigated using familiar songs. Their results showed that titles and melodies were easier to remember than lyrics. Although this advantage of melody over lyrics is at odds with the other studies on this issue (Crowder et al., 1990; Peretz et al., 2004a; Serafine et al., 1986), the authors suggest that this may be related to the use of very familiar songs in their study (as opposed to novel or unfamiliar songs) and the implementation of recall tests instead of recognition tests. Their results resonate with the popular impression that melodies are more often brought to mind than lyrics when recalling a song. Overall, melodies and titles were easier to remember than lyrics, but lyrics were in turn better cues. In other words, although less easy to remember, lyrics evoked melodies more often than melodies or titles evoked lyrics. This evidence suggest an integrated representation of songs, since titles – information that is not necessarily within the perceptual representation of the song, but rather label it – were not as efficient as lyrics in cueing melodies.

An alternative factor that can account, however, for this effect, is that melodies are often repeated several times over changing lyrics within a song. Such repetitive exposure may strength the memory trace for the melody in the long term, resulting in the reported recall advantage. On the other hand, the primacy of linguistic processing, for which very subtle differences are coded automatically, may explain the advantage of lyrics over melodies when novel songs are learned and in recognition. Observations in expert musicians, who process music in a high analytic level – in a similar way as language is commonly processed – point to this idea (Tervaniemi et al., 2001; Williamson et al., 2010).

It is worth noting that the studies discussed here differ qualitatively from other studies looking at source memory in which memory for words/sentences is studied in different auditory environments including music. Although those studies also delve into music and language associations, they differ to song events, as they may not result in a bound representation that merges all the information in a unified percept. However, some of the results from the interplay of verbal and musical information may be applicable to the context of song memory.

Music background has been shown to facilitate verbal encoding as compared to silence (Ferreri et al., 2013). The authors link this effect to the richness of the encoding environment, which would be responsible for the reduced demand on the dorsolateral prefrontal cortex. Extrapolating this finding to song research, sung lyrics could be understood as richer stimuli than spoken lyrics, and thus, a similar benefit could be found for song encoding as compared to spoken text. This idea is able to accommodate data from Alzheimer's disease patients showing that, although the initial learning of the text was easier when only spoken, sung lyrics produce more robust consolidation of verbal memory than spoken lyrics alone (Moussard et al., 2012). A similar benefit on memory for sung as compared to spoken presentation of the Rey Auditory Verbal Learning Test (RAVLT) has been recently reported in patients with multiple sclerosis (Thaut et al., 2014), further suggesting that songs boost deep encoding with consequent benefits on verbal memory. Studies on song memory in patients with temporal lobe lesions will be revised in the following section.

Studies with patients

Despite the vast evidence for the integrated processing of songs in healthy participants, data from lesion studies supporting independent processes cannot be dismissed. One of the most well-described examples of dissociation between music and language processing has come from the study of individuals with acquired or congenital musical impairment (amusia) as compared to patients with aphasia (McChesney-Atkins et al., 2003; Peretz et al., 2004b; Terao et al., 2006; Tillmann et al., 2009; Peretz et al., 2012). Notably for the study of memory, patients with temporal lobe damage have revealed there to be dissociations in the recognition of lyrics and melodies in songs (Hébert and Peretz, 2001; Samson and Zatorre, 1991).

Borrowing the paradigm from Serafine and colleagues (Serafine et al., 1984, 1986; Crowder et al., 1990), Samson and Zatorre (1991) assessed song recognition in patients after surgical removal of the anterior temporal lobe for the relief of intractable temporal lobe epilepsy. Recognition of songs as well as recognition of lyrics and melodies were tested in patients with left and right temporal lobe lesions as well as healthy controls. Songs and song elements had to be recognized within different kinds of songs: the *original* studied songs, songs with old lyrics and new melodies, old melodies and new lyrics, new songs, and old lyrics rearranged with old melodies from a different studied song. Comparisons between these conditions allowed the testing of the memory for each element as well as for their integrated representation.

The results showed impaired recognition of lyrics in patients with left temporal lobe lesions while recognition of sung melodies was shown to be impaired following right or left temporal lobe lesions. These data suggested that memory for lyrics depends on the left temporal lobe in line with the predominant role of the left hemisphere in verbal processing.

Nevertheless, two pieces of evidence also supported integration in this study (Samson and Zatorre, 1991). First, the significantly better recognition of *original* songs than *rearranged* songs, and second, the better recognition of melodies in *original* songs than in *rearranged* songs. However, words were similarly recognized in both conditions, which suggests that although text and melody are at some level integrated in memory for songs, words have some independence from the melody.

However, a caveat of this study lies on the small number of original (n=4) and rearranged (n=4) songs used in the recognition task and the precision of patients’ resections. Lesions extended over the lateral and the medial temporal lobe areas. Thus, it was difficult to identify the regions responsible for these effects, despite the authors did not find differences between resection limited to the anterior part of the MTL and resection extending to include large portion of the hippocampus in this particular sample. Anterior structures to Heschl's gyrus and the hippocampus, such as the amygdala or temporal pole were always removed, but the hippocampus, parahippocampal gyrus and Heschl's gyrus were resected to different amounts.

Unfortunately, to our knowledge this is the only study that has looked at memory for songs in a temporal lobe damaged population. However few other studies have investigated memory for music (Samson and Zatorre, 1992; Samson and Peretz, 2005; Wilson and Sailing, 2008). Although strong conclusions to song memory could not be directly extrapolated from studies on music without words, evidence from this research justify the study of the role of the right and left MTL structures in memory for song elements, an issue that is at the core of the current work.

Samson and Peretz (2005) assessed the effect of MTL lesions in musical preference and implicit recognition. Prior exposure to music has been shown to increase preference, an implicit memory effect that is not necessarily linked to explicit memory recognition (Peretz et al., 1998). Accordingly, both patient groups show explicit recognition deficit as compared to controls, confirming previous findings reported in Samson and Zatorre (1992). However, only controls and patients with left lateralized lesions preferred studied versus non-studied melodies, whereas patients with right lateralized lesions did not show this implicit exposure effect. This data supports the independence and right lateralization of music, as it suggests that right temporal structures play a decisive role both in priming and memory recognition of musical excerpts.

In another study, Wilson and Sailing (2008) examined the differential contributions of the right and left MTL for musical processing. Recognition memory was measured using two melodic learning tasks: one with tonal pairs and another one with non-tonal pairs. Results showed that both groups of hippocampal sclerosis patients had difficulties with non-tonal pairs but only the patients with right lesions showed a deficit in tonal pair learning, in line with those of Samson and Peretz (2005). This evidence suggests that the right hippocampus may be preferentially involved in melodic learning within a familiar music (tonal) context. Conversely, left hippocampus deficits suggest that this structure may be more engaged pitch interval processing.

Chapter 3: Binding songs - Aim of the thesis and research questions.

a. Aim of the thesis

The aim of this thesis is to investigate the binding of lyrics and melodies during listening and encoding of songs. As argued previously in this introduction, the relevance of addressing this issue goes well beyond music cognition itself, having on the one hand strong theoretical implications on the current memory models stressing the binding function, and on the other hand, on the use of music, particularly songs, to promote cognitive health in people with memory problems.

Although binding is not supposed to be modality-specific, most of the data on which memory models have been built come from the visual domain. This thesis proposes an original approach: applying binding principles to song memory. Therefore, it accounts for a strong auditory (temporal) component for binding that has been systematically neglected in the past. From this novel viewpoint, functional responses of MTL structures to song perception and encoding were investigated. Furthermore, an extended mechanism for binding concerning auditory information is proposed in which other structures involved in timing, sequencing and audio-motor coupling may cooperate with the hippocampus to support binding when auditory stimuli are involved.

Songs were chosen for the study of binding based on the ecological validity of the integration of verbal and musical features, but also based on the relevance of verbal memory in regard to re-education programs. Despite a number of studies that have recently highlighted the possible benefits of music for cognitive re-education in people with memory problems (Baird and Samson, 2014; Clément et al., 2012; Moussard et al., 2012; Narme et al., 2014; Palisson and Narme, in press; Särkämö et al., 2014; Thaut et al., 2014; for a review see Baird and Samson, 2015; McDermott et al., 2013; Raglio et al., 2012; Ueda et al., 2013; see also Annex B), research remains insufficient to describe the brain mechanisms that may underlie such benefits. In this sense, this thesis attempts to maintain an applied prospective goal, with the idea that better understanding of music binding processes may help us to improve the assessment and support of people with memory problems, as for instance temporal lobe epilepsy patients, dementia patients, or elderly people presenting cognitive decline. Specifically, the present research focuses on the role of the MTL on binding lyrics and melodies following the presentation of new unfamiliar songs.

b. The key research questions

It may be argued that it is increasingly important for studies examining the nature of songs to investigate the integration of lyrics and melodies at different levels of cognition if they aim to capture the complexity of the emergence of a song memory trace. The study of binding in other domains has determined a role for the MTL in such integrative processes, from perception to memory, that give rise to the encoding of a unified objects or event percept. To examine the MTL role on the binding aspects of song memories, three main questions were addressed in this thesis.

The first research question "*Can a hippocampus lesion disrupt the integrated percept of new unfamiliar songs?*" focuses on the effects of hippocampal sclerosis on perceptual binding in songs as attested by neural adaptation to song repetitions (**study 1**). Adaptation patterns to lyrics, melodies, and an integrated representation of song in patients were compared to healthy controls.

The second "*Is the hippocampus involved in binding lyrics and melodies for the encoding of songs? What other structures may also be involved?*" and third research questions "*Is there a difference between unified and separate presentation of lyrics and melody for song encoding?*" were then addressed by **study 2**. The second research question of this thesis evaluated the involvement of the hippocampus during song encoding and the additional implication of other brain structures in this particular form of binding. Building on this, the third research question formulated a differential involvement of the hippocampus and the new purposed structures following the separate or unified presentation of lyrics and melodies during encoding.

Finally, the fourth research question "*How does a temporal lobe lesion including the hippocampus affect song recognition?*" raises the impact of temporal lobe lesions including the hippocampus on song recognition (**study 3**). The song recognition task from **study 2** was adapted to test patients behaviorally on the binding of lyrics with their melodic context as compared to a healthy control group.

These research questions will be now briefly introduced before being described in further detail in the forthcoming chapters of the experimental part of the thesis.

i. Perceptual binding of songs – Can a hippocampus lesion disrupt the integrated percept of new unfamiliar songs?

Songs form unified representations that combine lyrics and melodies. Research in song perception has described a network involving the temporal lobe cortex, SMA and the cerebellum. Although some perceptual aspects of lyrics and melodies are processed independently, few studies in healthy participants have shown that posterior areas of the STG support the integrated percept of songs. In other words, an auditory object emerges from the perceptual binding of lyrics and melodies that is different from the two components taken in isolation. However, the mechanisms allowing for the representational binding of these two song components during song perception remain unclear.

According to the binding literature, the hippocampus is engaged in binding stimulus features into a single percept, and this may also be the case for the binding of lyrics and melodies. To address this issue, we investigated cerebral responses of patients with hippocampal sclerosis to song repetitions in an fMR-adaptation paradigm previously used with healthy participants (Sammler et al., 2010). This paradigm was chosen because it is based on the interface between memory and perception, tapping therefore into the emergence of a representation that can become a memory trace. This process is thought to rely on the MTL function, which is damaged in our patient population.

Nevertheless, the key role of the hippocampus in song perceptual binding remains to be tested and is an important outstanding issue, which the current thesis seeks to address.

ii. Memory binding for songs (fMRI) – Is the hippocampus involved in binding lyrics and melodies for the encoding of songs? What other structures may also be involved?

Songs naturally bind lyrics and melody into a unified representation. Nevertheless, although learning and remembering songs is rather common, the cerebral bases underlying binding for lyrics and melodies have received little attention.

Based on studies in non-musical domains, the MTL structures are here delineated as suitable candidates to support lyrics and melodies binding. However, when incorporating important variables that affect audition, and particularly music, such as temporal dynamics, a larger network including the IFG, basal ganglia and cerebellum may be involved in song binding.

The present thesis supports and discusses the role of the hippocampus in binding lyrics and melodies for song encoding. However, it also argues for the involvement of other structures such as the basal ganglia, the cerebellum and the angular gyrus, which seem to be important for the binding of auditory information.

iii. Memory binding for songs (fMRI) – Is there a difference between unified and separate presentation of lyrics and melody for song encoding?

To address binding of lyrics and melodies for song encoding, we compared BOLD signal changes during subsequent encoding of songs under unified and separate conditions. In both conditions, participants were instructed to generate mental images of the songs and to rehearse them covertly until the next trial. BOLD signal during encoding was analyzed using a GLM and a parametric approach taking subsequent memory for each encoding trial into account. Furthermore, correlations between brain activity and memory performance overall in the regions of interest (MTL subregions, IFG, and basal ganglia) were examined.

Based on previous findings in the visual literature (Staresina and Davachi, 2009), we hypothesize that the separate presentation of lyrics and melodies for song encoding (separate condition) will require a higher involvement of the hippocampus than the unified presentation (unified condition), since the integrated unified representation is not initially given and instead needs to be created. Beside the general mechanisms for song binding assessed by the first question, this issue is interesting in itself. Since during both conditions participants are covertly rehearsing a song, differences between conditions are mainly driven by the stimuli presentation characteristics and the consequent differences in the generation of a song representation.

On one hand, the unified presentation provides a richer auditory object that may facilitate encoding and retention. It is worth noting that, at this level of processing, unification of verbal information has been reported in Broca's area. If the weight of lyrics is such, that melodies are processed as a characteristic of the lyrics, then encoding of binding for unified songs may be at least partially sustained by the left inferior frontal lobe.

On the other hand, the separate presentation requires higher cognitive demands, since the integrated representation need to be created online by participants. Therefore, we expected the separate condition to require greater activation of several brain areas including the hippocampus, the striatum and the inferior parietal lobe, as opposed to passive binding.

Comparing these two conditions, the current thesis seeks to explore the binding of song elements from two different stimulation perspectives, highlighting the qualitative difference between a unified song and the mere combination of lyrics and melodies from the same song.

iv. Memory binding for songs (Neuropsychology) – How does a temporal lesion including the hippocampus affect song recognition?

For a song to be remembered, lyrics and melodies need to be bound into a unified mental representation. A vast number of studies have shown that memory-binding processes are related to hippocampal function. However, the role of the hippocampus in the binding of songs remained to be established. To complement the previous fMRI study, we conducted a neuropsychological study that investigates the effects of unilateral temporal lobe lesions including the hippocampus on binding lyrics with their melodic context in memory. Patients with right (RTL) or left (LTL) temporal lobe lesions were tested in a song recognition task, in which original songs had to be recognized among rearranged songs (wrong combination of old melodies with old lyrics from another studied song), and new-lyrics songs (new lyrics with old melodies). Given that both old lyrics and old melodies were presented in original and rearranged songs, this paradigm allows for the specific examination of binding by comparing recognition of these two types of songs. Based on results form **study 2**, and previous studies with similar patients (Samson and Zatorre, 1991), a deficit in lyrics recognition was expected for LTL, whereas a deficit in binding lyrics with the memory context was predicted for both LTL and RTL. Results are discussed in light of previous neuroimaging findings and theoretical contexts that favor the specific contribution of the hippocampus in binding lyrics and melodies in songs. Further by accompanying neuroimaging investigations on healthy participants with this neuropsychological assessment of patients, the current thesis seeks to provide a rich account of song memory binding.

Experimental part

Chapter 4: General methodological considerations

Although the specific methods used for each experiment will be described in detail for each study in the specific correspondent chapter, here general methodological considerations that apply to the whole of this work are drawn. I will provide a brief background on our patient population, temporal lobe epilepsy patients, and the neuroimaging methods used, namely functional Magnetic Resonance Imaging (fMRI). This section will introduce fMR-adaptation, the subsequent memory paradigm and the logic of the region of interest (ROI) analysis. Additionally the instrumental use of song imagery for the study of binding will be discussed.

a. Medically intractable temporal lobe epilepsy

Temporal lobe epilepsy is a common neurological disorder characterized by seizures arising from the MTL, most of the times with the epileptogenic focus in the hippocampus. Thirty percent of the epilepsy are refractory to the pharmacological treatment, and therefore, candidate for surgical removal of the epileptic focus. These resections are very successful to control seizures, which in turn can ameliorate the general cognitive performance by eliminating distal negative influence from the epileptogenic area and medication. Nevertheless, loss of the damaged area of the MTL and the disruption of certain connections can be responsible for memory impairment.

Advancement and development of new techniques that could assess different cognitive functions affected by the area to be removed in presurgical candidates, are required to improve prediction of surgical outcome to better evaluate the possible benefits of this treatment and to plan rehabilitation strategies (Dupont et al., 2010; Baxendale, 2008 Helmstaedter et al., 2008). In the present thesis, we examined patients with unilateral temporal lobe lesion before and after the surgical treatment of their epilepsy.

i. Pre-op

Patients that have participated prior to the operation help us to understand the impairments already produced by the epileptic activity, in our case, always associated with hippocampal sclerosis that resulted in a considerable reduction of hippocampus volume and function. Although the lesion in this population is in someway more localized, it is worth to keep in mind that the epileptic activity can damage also the connection between regions, thus affecting distal areas that have no apparent lesion (Besson et al., 2014). Thus, any result concerning this patients needs to be cautiously interpreted.

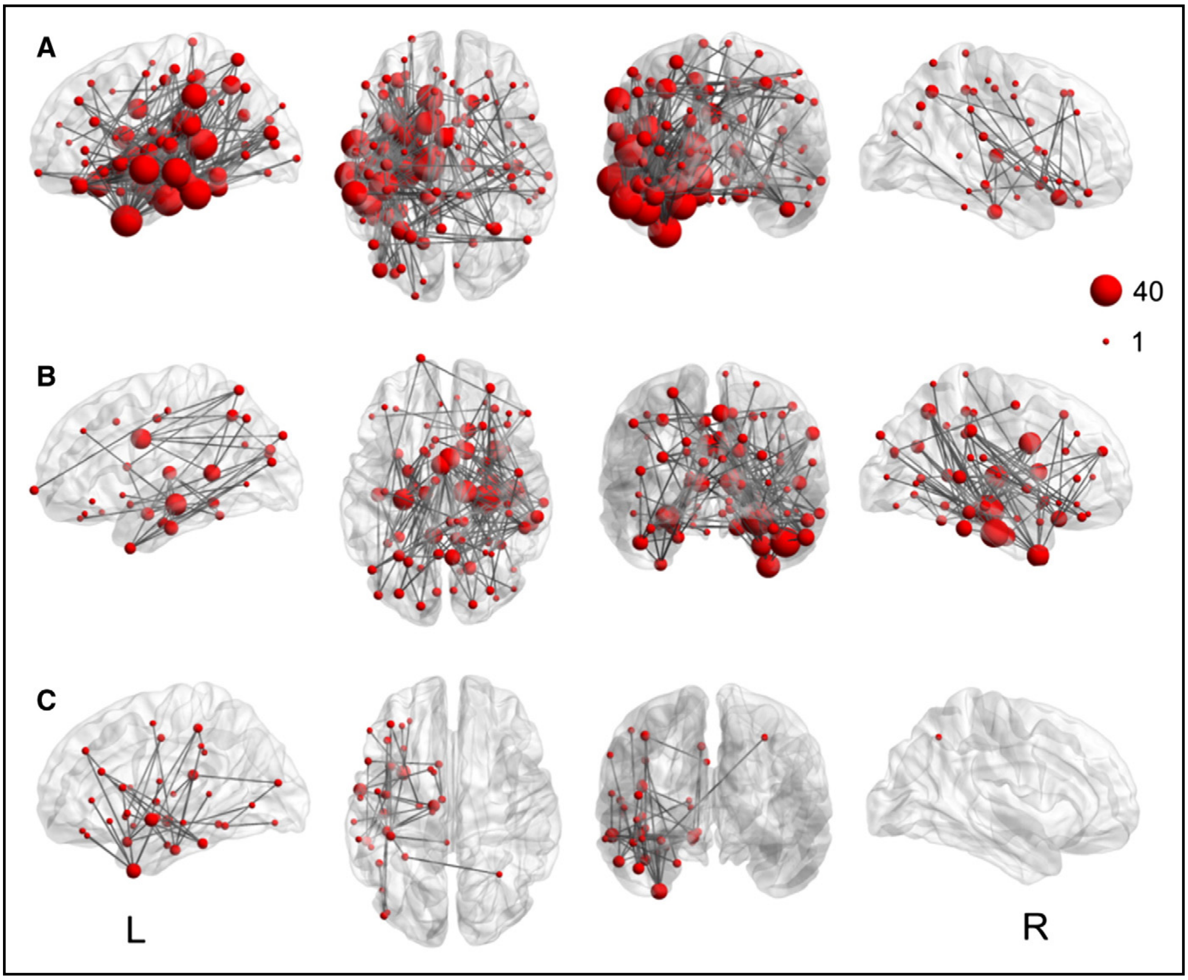

Figure 8. Network based statistics from Besson and colleagues (2014). Diminished connectivity strength in left TLE (A) and right TLE (B) as compared with control subjects with regard to the largest coherent cluster. Decreased connectivity in left TLE with respect to right TLE patients (C). The direct comparison yielded a fronto-temporal network component disconnected in left TLE. Black lines, representing diminished connectivity strength between nodes, form an interconnected cluster. ($p < 0.05$ FDR corrected).

ii. Post-op

The assessment of patients after the operation, gives a different insight. The surgical removal in the patients that participated in our studies, always included the hippocampus, but other areas of the medial and anterior temporal lobe. The evaluation of patients with right or left MTL resection helps us to look at lateralization differences in hippocampus-temporal lobe function, and also on the assessment of the remaining functions after the operation.

The lesion studies involving temporal lobe epilepsy patients examined during pre or post surgical evaluation, not only give us hints on the function of the damage areas, but also about the remaining capacities that can later serve the patients for re-education of some of the impaired functions.

b. fMRI

Functional Magnetic Resonance Imaging (fMRI) is non-invasive neuroimaging technique that allows the visualization of brain activity during different behavioral tasks. The experiments in the current thesis have being carried out in an MRI scanner that generates a magnetic field of 3 Tesla field strength.

The oxygen in the blood is susceptible to this magnetic field. Nuclei of H_2O atoms in the blood will align with the magnetic field. The MRI machine measures this directional change. When a region in the brain is active, neuronal activity triggers metabolic consumption, increasing the blood flow and thus the intensity of the measured signal. The brain regions are activated by different tasks, such as for instance, listening to music. Cognitive neuroscience measures the involvement of brain regions in a variety of behavioral tasks indirectly though blood oxygenation level dependent (BOLD) changes.

We use fMRI during listening and encoding songs to identify regions engaged in processing lyrics, melodies and the integration of them in perception and memory. Although the detailed methods used for each experiment will be specified in the “methods” section of each study in the following chapters, here I describe a brief background on the two main paradigms that will be used, namely fMR-adaptation and subsequent recognition.

i. fMRI adaptation

As described by Grill-Spector et al. (2006), adaptation is a reduction of neural activity following prolonged or repetitive exposure to identical or at least similar stimuli. Neural adaptation or repetition suppression (Krekelberg et al., 2006) is a neuroimaging effect similar to repetition priming (Old vs. New stimuli), but requires a successive presentation of changed or unchanged stimuli (Same vs. Different stimuli) (Dobbins et al., 2004; Ganel et al., 2006). The adaptation effect expressed by a reduction of activation mainly in cortical structures has been mostly used to study perception (Grill-Spector and Malach, 2001). However, the repeated presentation of a stimulus has also a mnemonic impact that can induce adaptation within MTL structures (Henson, 2003). This procedure, which is particularly well suited to explore the cortical network underlying the processing of lyrics and melodies in songs, was adapted to music for the first time by Sammler and colleagues (2010).

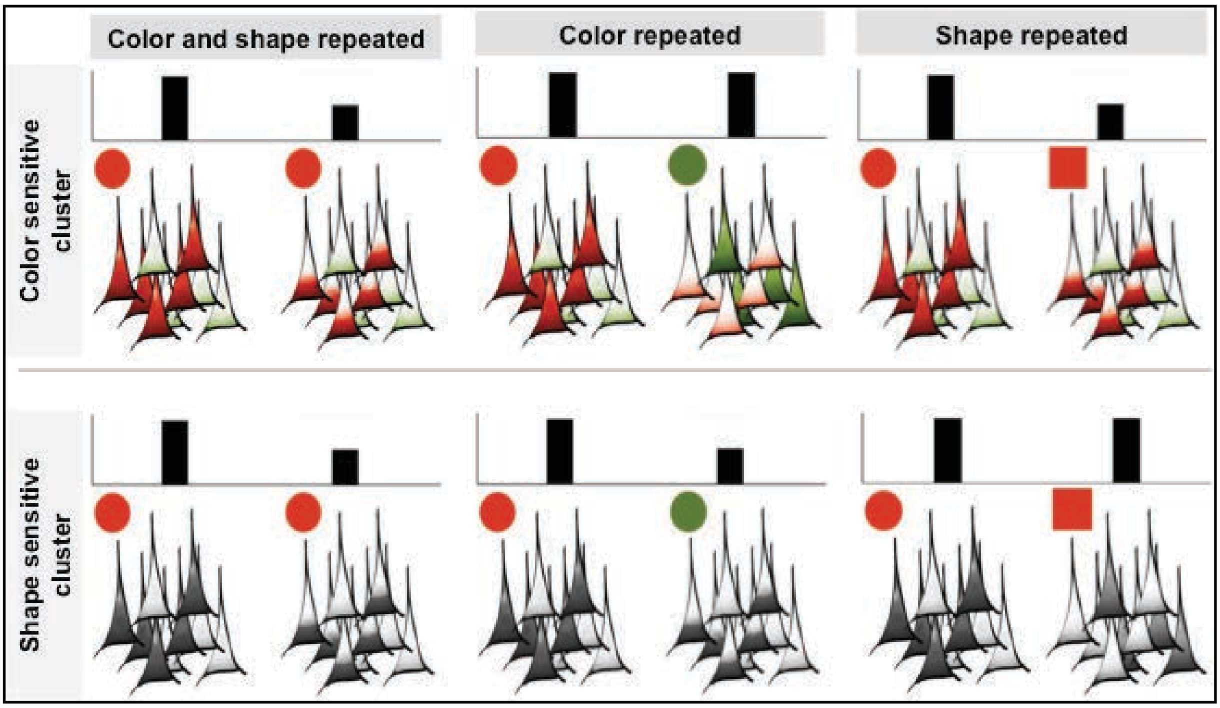

Figure 9. Schematic illustration of neural adaptation for color and shape. A cluster of neurons in a voxel that is sensitive to color (upper row) would reduce its activity following the repeated presentation of the same color. A cluster of neurons in a voxel that is sensitive to shape would reduce its activity following the repeated presentation of the same shape.

b. fMRI

Adaptation paradigms have been widely applied in the visual field to explore adaptation with pictures (Blondin and Lepage, 2005; Goh et al., 2007; Grill-Spector and Malach, 2001), faces (Grill-Spector and Malach, 2001; Johnson et al., 2004; Sperling et al., 2003; Winston, 2004) and words (Chee et al., 2003; Chee, 2009; Noppeney and Price, 2004). In the auditory domain, fMR-adaptation paradigms have been used to investigate reduction of cortical activity using environmental sounds (Bergerbest et al., 2004), spoken language (Dehaene-Lambertz et al., 2006; Klein et al., 2006; Santi and Grodzinsky, 2010), voices (Belin and Zatorre, 2003), and songs (Sammler et al., 2010).

ii. Subsequent memory paradigm

The subsequent memory paradigm is one of the most widely used paradigms to address episodic encoding with fMRI (Brewer et al., 1998; Kim et al., 2011; Wagner et al., 1998). The main assumption of this paradigm is that differences in brain activity during encoding predict later success during the recognition test. Consequently, recognition scores can be used to sort and compare encoding trials, showing brain correlates of successful encoding, or as traditionally named “difference due to memory”. Although originally developed to analyze ERPs (Paller et al., 1987), the subsequent recognition paradigm was soon applied to fMRI (Brewer et al., 1998; Wagner et al., 1998) and remains one of the most powerful and successful tools to address encoding (Paller and Wagner, 2002).

The experimental procedure following this paradigm includes two main phases: a study or encoding phase, and a test or recognition phase. During the study phase, participants are scanned while studying a series of stimuli for a latter recognition test. During the test phase, participants have to recognize studied stimuli among other new lures, and therefore they classify stimuli as old or new. The most relevant innovation of this procedure is that then, recognition responses for the studied material are used to backsort trials for the analysis of BOLD signal changes in the study phase. Trials of items that were later correctly recognized become “subsequently remembered” trials, and those that are missed become “subsequently forgotten” trials. The comparison of BOLD changes between subsequently remembered trials and subsequently forgotten trials displays the “difference due to memory”, or as it is more often reported successful encoding effects (Brewer et al., 1998; Davachi and

Wagner, 2002; Fletcher et al., 2003; Kim et al., 2011; Kirchhoff et al., 2000; Morcom et al., 2003; Otten et al., 2001; Rypma and D'Esposito, 2003; Wagner et al., 1998).

For example, in the study phase of a subsequent memory paradigm as applied by Staresina and Davachi (2009), participants were presented with images of one of four colors in different conditions: "a red mug", “a blue shirt” "a green grape cluster", etc. Following the study phase, participants had to complete a recognition test in which those objects were presented along with other new objects. Participants had to judge if the objects presented during recognition were new or old, then, if “old”, they had to identify the color that was associated with each object, and finally give a confidence rating of their response. When a subject correctly classifies "a mug" as old, it becomes a subsequently remembered trial. Conversely, when a subject incorrectly judges "a shirt" as new, it becomes a subsequently forgotten trial. The neural activity elicited by the presentation of "a mug" along with all other subsequently remembered items and "a shirt" along with all other subsequently forgotten items at the study phase is then compared and the successful encoding effect is derived from this comparison.

It is worth mentioning that this example intentionally includes a second level of encoding: besides the subsequent memory for the object, there is also the subsequent memory for the binding of it with its context. To this extent, the authors show that successful encoding engages the hippocampus to a greater extent when the contextual information of an item is bonded in the memory trace. The role of confidence ratings here is to provide putative weighting of the recognition by which high confidence correct responses are interpreted as a result of recollection, whereas low confidence ratings remain less interpretable as they may be confounded by familiarity processes. Therefore, most studies keep high confidence correct items as “subsequent recognized trials” and keep low confidence correct items aside and even sometimes as “subsequently forgotten” trials. However, a caveat on this approach is that people use different responding style, being more or less conservative, so confidence responses may have been given in a different basis than the recollection/familiarity assumption.

From a behavioral standpoint, the combination of accuracy and confidence of recognition responses has been used to provide a more sensitive analysis of recognition, assuming that higher confidence may also respond to a stronger or richer memory. To compute this combined measure, the principles of signal detection have been applied to recognition using Receiving Operating Curves (ROCs) (Yonelinas et al., 1996, Yonelinas and Park, 2007). The area under the curve (AUC) can be then used as a dimensional measure of recognition success (Yonelinas and Park, 2007). In the presented work, an innovative tempt to combine this two approaches has been done by including a parametric analysis of fMRI encoding data on the basis of AUCs (see **Chapter 6**).

iii. Region of interest (ROI) analysis

Statistical analysis within Statistic Parametric Maps (SPM) is based on a statistic test on every single voxel of the brain. Thus, the likelihood of finding a false positive difference, namely the Type I error, is very high given the great number of tests. When the hypotheses of a research question are anatomically constrain, it is becoming regular to apply a region of interest (ROI) approach. This analysis delineates the regions of the brain that are of interest for the hypothesis that will be tested, and restricts the statistical test to those regions. Beta values within that given region are averaged, thus significantly reducing the number of tests as compared to the single voxel approach of SPMs.

ROIs are often drawn on anatomically defined regions, although they can also be confined to specific areas previously selected by the experimenter for their functional involvement in an independent study or analysis. Thus, it is assumed that the activity within the ROI will respond to the same function, justifying in this way the joint analysis of all voxels within the region. Consequently, the ROI analysis allows a more sensitive exploration of relevant areas controlling for Type I error (Poldrack, 2007).

c. Song imagery

In the present scientific work, song imagery will be more a tool than an object of investigation itself. Imagery will be used to study the encoding of songs, based on the evidence presented in **Chapter 1**.

Although the mere existence of imagery was traditionally a source of debate in psychology (Watson, 1913), the cerebral substrate of imagery has been increasingly explored during the last three decades thanks to cognitive neuroscience and neuroimaging methods

(Behrmann, 2000; Kosslyn et al., 2001). When characterized as a mental representation, aspects of imagery have been compared to perception, and indeed, similar brain networks have been shown to be active during both processes (Halpern, 2001; King, 2006; Kosslyn et al., 2001; Vlek et al., 2011). Mental imagery has been shown to recruit similar areas to those activated by a perceptual correlate. For instance, Kosslyn and collaborators (1997) found that perception and imagery of visual stimuli overlaps in around two thirds of the recruited areas. However, perception and imagery also differ in certain aspects, as it suggested by double dissociations found in neuropsychological assessment of brain damaged patients (Bartolomeo et al., 1998; Bartolomeo, 2002; Behrmann et al., 1992, 1994).

In perception, the stimuli are physically present, whereas its absence defines mental imagery. From a computational perspective, the first relies more on a bottom-up process whereas the latter relies on a top-down process. Thus, perception requires low-level organization processing while imagery needs information from memory and requires a bigger cognitive effort (Bartolomeo, 2002). This idea is coherent with the greater activation observed during imagery, of areas such as the hippocampus or the inferior frontal gyrus, or other multimodal associative areas highly linked to the limbic lobe such as the angular gyrus or the supramagial cortex (Ishai et al., 2002).

From another viewpoint, imagery has also been compared to memory, since retaining information, as is done by working memory, or remembering past events, requires some sort of mental re-experience of that memory trace (Hassabis et al., 2007; Martin et al., 2011; Race et al., 2011; Slotnick et al., 2012). For instance if you were to remember your last holiday abroad, you would probably experience some visual scenes and “re-experience” aspects of the journey, as if you were imagining that particular place. Similarly if you were asked to recall the song “imagine” by John Lennon, you could probably listen to it in your head.

It is worth noting that different modalities of imagery require different networks in the same way that they lie on different perceptual and memory systems that may at the same time be stimulus specific, such as memory for faces, verbal memory, or procedural memory. For instance, motor imagery has shown to activate parietal cortex, premotor cortex, primary cortex, and supplementary motor cortex (Filimon et al., 2007) in mental rotation tasks.

c. Song imagery

One advantage of imagery is that participants are not required to produce the images they recall. That is, that one can imagine the Colosseum in Rome while being unable to draw it, or the aria Nessun Dorma without being able to successfully sing it, because that experience of imagination is closer to perception (or is somewhere in between) than production. Of course, a more profound degree of knowledge of the detail of the imagined object would result in more vivid mental imagery, so expertise could be a factor that enhances the degree of “re-experience” produced by mental imagery, also in music (Herholz et al., 2008).

In this sense, the ability of mental imagery provides us with the capacity to create representations of previously experienced representations, but furthermore, also never experienced or realistically impossible, such as, for instance, imagining a purple elephant. This last characteristic makes imagination suitable for the study of the binding function.

Chapter 5: Hippocampal sclerosis affects fMR-adaptation of lyrics and melodies in songs.

Hippocampal sclerosis affects fMR-adaptation of lyrics and melodies in songs

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Hippocampal sclerosis affects fMR-adaptation of lyrics and melodies in songs

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Songs constitute a natural combination of lyrics and melodies, but it is unclear whether and how these two song components are integrated during the emergence of a memory trace. Network theories of memory suggest a prominent role of the hippocampus, together with unimodal sensory areas, in the build-up of conjunctive representations. The present study tested the modulatory influence of the hippocampus on neural adaptation to songs in lateral temporal areas. Patients with unilateral hippocampal sclerosis and healthy matched controls were presented with blocks of short songs in which lyrics and/or melodies were varied or repeated in a crossed factorial design. Neural adaptation effects were taken as correlates of incidental emergent memory traces. We hypothesized that hippocampal lesions, particularly in the left hemisphere, would weaken adaptation effects, especially the integration of lyrics and melodies. Results revealed that lateral temporal lobe regions showed weaker adaptation to repeated lyrics as well as a reduced interaction of the adaptation effects for lyrics and melodies in patients with left hippocampal sclerosis. This suggests a deficient build-up of a sensory memory trace for lyrics and a reduced integration of lyrics with melodies, compared to healthy controls. Patients with right hippocampal sclerosis showed a similar profile of results although the effects did not reach significance in this population. We highlight the finding that the integrated representation of lyrics and melodies typically shown in healthy participants is likely tied to the integrity of the left medial temporal lobe. This novel finding provides the first neuroimaging evidence for the role of the hippocampus during repetitive exposure to lyrics and melodies and their integration into a song.

Keywords: neural adaptation, song, lyrics, hippocampal sclerosis, memory trace, conjunctive representation

INTRODUCTION

As humans, we learn and enjoy songs from a very early age on. Over the course of our lives, we hear and remember thousands of songs and, most of the time, we learn them implicitly without much effort especially after repeated presentations (as with hit songs on the radio). Songs naturally combine music and language into a unique acoustic signal. However, it remains unclear whether memory traces of lyrics and melodies are built separately or in integration. Indeed, evidence from healthy participants and brain-damaged patients diverge on this question. On the one hand, several behavioral studies in healthy participants support the tight association of lyrics and melodies during the creation of a song memory trace as shown by cueing effects of one element on the other during song recognition (Serafine et al., 1984, 1986; Crowder et al., 1990; Baur et al., 2000; Peretz et al., 2004; Peynircioglu et al., 2008; Johnson and Halpern, 2012). On the other hand, neuropsychological studies in patients with lesions in the medial or lateral temporal lobes reveal dissociated recognition impairments for verbal and musical features of songs (Samson and Zatorre, 1991; Hébert and Peretz, 2001). These results suggest that the natural binding of lyrics and melodies into one unique song memory trace may be disrupted after brain damage. The present study seeks to find neural evidence for this hypothesis by investigating the effect of hippocampal damage on the emergence of integrated memory traces for lyrics and melodies during repeated exposure to songs.

Research over the last two decades testifies to a growing awareness that the hippocampus – beyond its classical role in explicit episodic memory (Scoville and Milner, 1957; Mishkin, 1982; Zola-Morgan and Squire, 1993) – plays a role in the implicit build-up of a memory trace (Chun and Phelps, 1999; Graham et al., 2010) and the bridging between perception and encoding (Bussey and Saksida, 2005; Baxter, 2009; Suzuki, 2009; Suzuki and Baxter, 2009; Olsen et al., 2012). According to the Emergent Memory Account (Graham et al., 2010) advancing a non-modular view of memory and perception, memory arises from a dynamic interaction between the perceptual representations distributed across the whole brain and a key role of the medial temporal lobe. More specifically, the hippocampus is thought to form conjunctive representations of inputs from unimodal and polymodal sensory cortices and to continuously return the processed information to the sensory cortex via feedback connections (McClelland et al., 1995; Eichenbaum, 2000; Turk-Browne et al., 2006; Bast, 2007), thus constantly updating the current representations with new experiences. This cortico-hippocampal loop of flowing information guarantees the encoding of events and its storage (Eichenbaum, 2000). Note that this mechanism not only implies a shared, anatomically distributed cerebral network for both memory and perception, but also puts the medial temporal lobe into a cardinal position between perceptual processes (Lee et al., 2005; Lee, 2006; Lee and Rudebeck, 2010a) and memory (long-term as well as short-term and working memory: Zarahn, 2004; Axmacher et al., 2007; Lee and Rudebeck, 2010b; Rose et al., 2012). Crucially, the hippocampus' combined role in (i) memory formation and (ii) conjunction of sensory inputs (Sutherland and Rudy, 1989; Eichenbaum et al., 1994; Rudy and Sutherland, 1995; O'Reilly and Rudy, 2001; Winters, 2004; Cowell et al., 2006, 2010; Barense et al., 2007; Diana et al., 2007) makes it a potential key candidate for (i) the build-up of song memory traces, in which (ii) lyrics and melodies are integrated.

Although most of the studies on the hippocampus' role in memory formation and binding come from the visual domain (Davachi, 2006; Diana et al., 2007; Shimamura, 2010), we hypothesize that similar processes also apply to the auditory domain (Overath et al., 2007, 2008; Buchsbaum and D'Esposito, 2009), especially to songs. It is reasonable to assume that memory formation for lyrics and melodies happens through a cortico-hippocampal loop, and that the natural combination of a verbal and a melodic component into a single song percept and memory trace requires binding mechanisms as described above. Tentative support for this comes from lesion studies in patients with anterior temporal lobectomy for treatment of pharmaco-resistant epilepsy (Samson and Zatorre, 1991). Using explicit recognition memory tasks after presentation of short unfamiliar songs, these experiments revealed a clear deficit in recognition of sung and spoken lyrics after left temporal lobe resection, and impaired recognition of melodies (without text) after right temporal lobe resection. On top of that, the data suggest a lack of integration of lyrics and melodies in patients with unilateral left (but not those with right) temporal lobe lesions. While patients with right temporal lobe resections had deficits in melody recognition when the tune was sung with new words, i.e., showing that they had bound the melody to the original lyrics, no such conjunction was observed in left-hemisphere damaged patients. In fact, their recognition of lyrics was impaired irrespective of whether these were presented with (or without) old or new melodies, suggesting an independent processing of the two song components and an isolated deficit for lyrics.

While these results lend initial support for our hypothesis of hippocampal involvement in song memory formation, they leave two important questions open: first, in how far can these deficit patterns be attributed to hippocampal dysfunctions, and second, in how far may these results depend on the use of a recognition memory task? First, the resection always included anterior temporal lobe structures beyond the hippocampus, making it difficult to pinpoint a specific hippocampal role. Furthermore, although the lesion description was based upon the surgeon's meticulous drawings, a precise assessment of how far the resection extended into the hippocampus was not possible at that time. Moreover, although recognition tasks certainly depend on successful encoding, they also involve aspects of memory retrieval making it difficult to disentangle these effects with behavioral data. The present study seeks to address the points by first, testing patients with circumscribed unilateral hippocampal sclerosis (i.e., prior to surgery without further macroscopic lesions) and precisely describing the extent of hippocampal damage by means of volumetric analyses. Second, the incidental build-up of a song memory trace was assessed unbeknownst to the participants by examining the dynamics of neural adaptation during natural passive listening as described below.

Numerous studies have investigated the neural correlates of song processing (Samson and Zatorre, 1991; Brown et al., 2004a,b; Schön et al., 2005; Callan et al., 2006; Suarez et al., 2010; Merrill et al., 2012; Saito et al., 2012; Tierney et al., 2012), however, rarely has any study touched upon the implicit emergence of song memory. Indirect evidence can be drawn from studies using the successive presentation of changed and unchanged song stimuli (Same vs. Different) (Schön et al., 2010) and neural adaptation paradigms (Sammler et al., 2010). Adaptation is "a reduction of neural activity following prolonged or repetitive exposure to identical or at least similar stimuli" (Dobbins et al., 2004; Ganel et al., 2006; Grill-Spector et al., 2006), similar to repetition priming (Old vs. New stimuli) (Krekelberg et al., 2006). Although typically described in studies on perception, it appears that neural adaptation may also be indicative of memory trace formation. In line with the Emergent Memory Account (Graham et al., 2010), neural adaptation may reflect the emergence of a memory trace within cortical areas of perceptual representation through implicit learning during repeated exposure. Given the role of the hippocampus in memory formation (Turk-Browne et al., 2006) and according to connectionist models of memory (Damasio, 1989; McClelland et al., 1995; Rolls, 1996; Fuster, 1997), it is reasonable to suggest that cortical adaptation effects are subject to top-down modulations driven by the hippocampus (Blondin and Lepage, 2005; Goh et al., 2007), including integration of lyrics and melodies through binding (for a review on binding, see Opitz, 2010).

Of particular relevance for our research question of how lyrics and melody are bound in a conjunctive song memory trace are those studies describing the cerebral substrates underlying the integration of verbal and melodic components of songs (Sammler et al., 2010; Schön et al., 2010). These studies, which consider songs to be more than the sum of lyrics and melodies, examined modulations of brain activity to investigate how the two components interact, and how their processing is lateralized. For instance, Schön et al. (2010, Exp. 2) presented pairs of sung words that could vary or repeat in terms of the verbal and/or the melody component in a same-different task. Their results showed interactive processing in the left and the right superior temporal gyrus (STG), suggesting an integrated processing of the two components in these areas. Sammler et al. (2010) adopted a similar approach, taking advantage of neural adaptation effects. In this study, healthy participants were presented with blocks of short songs in which

Table 1 | Demographic data.

Group	*N*	Sex (males/females)	Mean age	Mean education	Musical expertise	Full scale IQ WAIS-R[a]	RAVLT forgetting%[a]
Control	19	9/10	32.63 ± 7.90	14.53 ± 2.99	5.02 ± 3.68	–	
LTLE	12	5/7	34.17 ± 8.71	12.25 ± 1.42	6.75 ± 4.46	92.66 ± 1.33	20.56 ± 22.99
RTLE	12	5/7	39.92 ± 1.23	12.67 ± 2.71	6.83 ± 5.45	95.43 ± 1.79	9.07 ± 10.76

[a] *Mean for all except two RTLE patients due two missing data. RAVLT: Rey Auditory Verbal Learning Test.*

repetition of lyrics and/or melodies was varied in a factorial design to induce selective adaptation to lyrics, melodies, or unified songs. Consistent with Schön et al. (2010), repeated lyrics or repeated tunes evoked adaptation effects in bilateral STG. Core areas of integration were found in the left middle superior temporal sulcus (STS) and the left premotor cortex (PMC). Based on the previously reported literature, we hypothesize that these adaptation effects and the integration of lyrics and melodies are likely mediated by the hippocampus through feedback connections to STG/STS and binding of verbal and melodic information.

To investigate the modulatory effect of the hippocampus on (i) the incidental emergence of a song memory trace and (ii) the integration of the verbal and melodic components of songs, we adopted the paradigm by Sammler et al. (2010) to test patients with unilateral left or right hippocampal sclerosis and healthy controls. We compared the patterns of adaptation produced by songs in which either the lyrics, or the melodies, or both were repeated. As demonstrated by diffusion-weighted imaging studies, patients with hippocampal sclerosis present disconnections between medial and lateral temporal lobe regions (Focke et al., 2008; Bettus et al., 2009; Diehl et al., 2010; Riley et al., 2010; Liao et al., 2011). Such lesions have the capacity to prevent the hippocampus from sending feedback predictions and from updating the sensory memory trace (as expected by default after repetitions) and thus weaken adaptation effects in general and integration of lyrics and melodies in particular. More precisely, following Samson and Zatorre (1991), we hypothesized reduced adaptation for lyrics after left and for melodies after right hippocampal sclerosis. Moreover, following previous studies showing binding deficits in patients with left anterior temporal lobe resections (Samson and Zatorre, 1991) and correlates of lyrics–melody integration mainly in the left hemisphere (Sammler et al., 2010), we hypothesized that left hippocampal lesions, in particular, would have a negative impact on integration of lyrics and melodies in songs.

MATERIALS AND METHODS

PARTICIPANTS

Twenty-four temporal lobe epilepsy patients with left ($n = 12$; LTLE) or right ($n = 12$; RTLE) hippocampal sclerosis participated in this study. They all presented with medically intractable epilepsy and were seen during pre-surgical evaluation at Pitié-Salpêtrière Hospital (Paris, France). All patients were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971), except for one LTLE (−83.33) and one RTLE patient (−75). All patients had language lateralization to the left hemisphere except for the left-handed RTLE patient with bilateral language representation. Language lateralization was assessed by means of a verbal fluency test that is part of the standard functional magnetic resonance imaging (fMRI) assessment prior to epilepsy surgery at the Pitié-Salpêtrière Hospital. In the scanner, patients are required to think as many words of a semantic category (e.g., tools) as possible. The number of activated left and right fronto-temporo-parietal voxels against baseline was used to calculate a standard language lateralization score (Lehéricy et al., 2000; Thivard et al., 2005). The control group consisted of 19 right-handed healthy participants including 12 subjects, who had already participated in a previous study (Sammler et al., 2010), and 7 new volunteers. All participants were French native speakers and reported to have normal hearing. Controls were carefully selected to match the patient groups in terms of age, mean years of education, and musical expertise (Ehrlé musical expertise questionnaire, unpublished). A verbal memory deficit was present in the LTLE as opposed to the RTLE patients, as assessed with the Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964; Sziklas and Jones-Gotman, 2008) in accordance with the usual neuropsychological profile of these patients. Demographic characteristics of the participants are summarized in **Table 1**. The sclerosis in either left or right hippocampus in the two patient groups was corroborated by a volumetric analysis using Freesurfer software (Fischl, 2012; Reuter et al., 2012) that attested an ipsilateral hippocampal volume reduction of an average of 24.51% in the LTLE and 29.71% in the RTLE group compared to healthy controls. Between-group comparisons confirmed the significance of these volume reductions in the atrophic hippocampus ($p < 0.05$). Volumes and percentage of reduction are summarized in **Table 2** (for details on the volumetric analysis, see Data Analysis). The local ethics committee approved this study and informed consent was obtained from each participant.

MATERIALS

The material and the scanning protocol used here were previously published by Sammler et al. (2010). The stimulus set consisted of 48 blocks of 6 unfamiliar songs based on a collection of nineteenth century French folk songs (Robine, 1994). Each song within a block was sung by a different singer to avoid adaptation to the singer's voice (Belin and Zatorre, 2003), had a duration of 2.5 s and was followed by a 0.2 s pause. Repetition of lyrics and/or melodies within blocks was crossed in a 2 × 2 factorial design, forming four conditions. Songs within a block either had the same melodies and same lyrics ($S_M S_L$), the same melodies but different lyrics ($S_M D_L$), different melodies with same lyrics($D_M S_L$), or different melodies and different lyrics ($D_M D_L$). Mode and tempo were balanced across the stimulus set, and each song had an average of 7.65 notes and 5.61 words. Songs in the four conditions did not differ with respect to length and number of word/note, word frequency, interval size, and number of contour reversals. In blocks where lyrics were varied, they did not rhyme, were semantically distant,

Table 2 | Medial temporal lobe (MTL) volumes (mm^3).

	Left MTL				Right MTL			
	LTLE		RTLE		LTLE		RTLE	
Region	Mean/ ± SD	Reduction (%)[a]	Mean/ ± SD	Reduction (%)[a]	Mean/ ± SD	Reduction (%)[a]	Mean/ ± SD	Reduction (%)[a]
Hippocampus	2606.17/506.82	24.51	3467.95/245.68	−0.46	3589.04/678.97	−2.72	2455.90/414.39	29.71
Entorhinal cortex	1802.67/613.03	3.86	1847.25/218.17	1.48	1901.42/408.28	3.73	1802/246.24	8.76
Parahippocampal gyrus	2165.42/386.72	8.56	2304.17/222.16	2.70	2249.92/266.37	3.26	2026/268.47	12.89

[a] *Percentage of reduced volumes as compared to control group volumes.*

and differed with respect to syntactic structure avoiding potential adaptation to phonology, semantic content, or syntactic structure (Noppeney and Price, 2004).

PROCEDURE

Participants were instructed to listen attentively with closed eyes while avoiding moving, humming, or singing along. No behavioral data were collected. Stimuli were presented using E-Prime 1.1 (Psychology Software Tools) and delivered binaurally through air pressure headphones (MR confon). Additionally, participants used earplugs to minimize noise interference. All blocks were presented in one of four pseudorandom orders, with a silent gap between blocks of 10 s (±0.5 s) allowing the hemodynamic response to return to baseline (Belin and Zatorre, 2003). This resulted in a total duration of the experiment of around 30 min. Blocks of the same condition were not presented more than twice in a row. At the end of the experiment, all participants filled in a debriefing questionnaire with several nine-point scales (1 = not at all, 9 = always) in which they rated their attention during listening at 7.63 (Controls), 7.00 (LTLE), 7.57 (RTLE), and the amount of overt and/or covert singing during scanning at 0.00 and 2.89 (Controls), 0.47 and 2.71 (LTLE), and 0.21 and 2.14 (RTLE), showing that they had followed the instructions.

SCANNING

Functional magnetic resonance imaging was performed using a 3-T Siemens TRIO scanner (Siemens, Erlangen, Germany) at the *Centre de Neuroimagerie de Recherche* at the *Institut du Cerveau et de la Moëlle Épinière – ICM* (Groupe Hospitalier Pitié-Salpêtrière, Paris, France). Radiofrequency transmission was performed with a body coil and the signal was received with a 12-channel head coil. Before the functional scans, high-resolution T1-weighted images ($1 \times 1 \times 1\ mm^3$ voxel size) were collected for anatomical coregistration using a magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequence (TR = 2300 ms, TE = 4.18 ms). Subsequently, one series of 595 blood oxygenation level-dependent (BOLD) images was obtained using a single-shot echo-planar gradient-echo (EPI) pulse sequence (TR = 2120 ms, TE = 25 ms, the first six volumes were later discarded to allow for T1 saturation). Forty-four interleaved slices (3 mm × 3 mm × 3 mm voxel size, 10% interslice gap) perpendicular with respect to the hippocampal plane were collected. The field of view was $192 \times 192\ mm^2$ with an in-plane resolution of 64 × 64 pixels and a flip angle of 90°. Scanner noise was continuous during the experiment representing a constant auditory background.

DATA ANALYSIS

The fMRI data were analyzed using SPM8 (Wellcome Trust Centre for Neuroimaging). Preprocessing included spatial realignment and reslicing and coregistration of the anatomical T1 to the mean functional data. The first level analysis was carried out in the native space. Four regressors were built for each experimental condition based on the general linear model (different melodies and different lyrics ($D_M D_L$); same melodies and different lyrics ($S_M D_L$); different melodies and same lyrics ($D_M S_L$) and same melodies and same lyrics ($S_M S_L$), and convolved with a hemodynamic response function (HRF). Movement parameters were included as regressors of no interest and serial correlations were modeled with an AR (1) process. A temporal high-pass filter with a cut-off of 200 s was used to eliminate low-frequency drifts. Six one-sample *t*-tests were computed for each participant: all conditions against silence to establish a "song-sensitive" mask, the main effects of adaptation to lyrics $[(D_M D_L + S_M D_L) - (D_M S_L + S_M S_L)]$ and to melodies $[(D_M D_L + D_M S_L) - (S_M D_L + S_M S_L)]$ to identify areas of general adaptation to the repetition of song components, as well as the interaction $[(D_M S_L + S_M D_L) - (D_M D_L + S_M S_L)]$ to isolate areas of lyrics–melody integration. For the sake of completeness and consistency with the analysis of Sammler et al. (2010), we additionally compared both main effects to identify brain regions that showed an independent processing of either lyrics or melodies (i.e., stronger adaptation for lyrics than for melodies $[2 \times (S_M D_L)]$ and vice versa $[2 \times (D_M S_L)]$).

Segmentation of the anatomical files was performed with the VBM8 toolbox (Ashburner and Friston, 2005) to form a normalized anatomical image and the DARTEL exported tissue types. A template with eight iterations was created in DARTEL (Ashburner, 2007) including all 43 subjects to improve anatomical accuracy in the normalization of the functional contrast images obtained in the first level. Contrast images were spatially smoothed using a three-dimensional Gaussian kernel with 8 mm full width at half maximum. For the second level, the DARTEL normalized contrast images were normalized to the Montreal Neurological Institute (MNI) space. The automatically generated mask from the first level analysis of each subject was also normalized with this procedure but without smoothing. Statistical analysis was confined to a song-sensitive mask in gray matter to increase signal detection (Friston et al., 1994). To create this mask, a binary mask from the last iteration of the DARTEL template thresholded at 0.3 was overlaid with active voxels in the "all conditions against silence" contrast at $p < 0.05$ (FWE correction for multiple comparisons), $k > 5$ for all 43 participants. All voxels that were involved in both were included into the explicit song-sensitive mask for statistics. This mask covered an auditory-motor network, including the temporal gyrus, the PMC, and the cerebellum. For random effects group analyses, the individual contrast images were submitted to one-sample t-tests, separately for healthy controls, LTLE and RTLE patients. Furthermore, two-sample t-tests were computed for all contrasts, comparing each patient group against controls. All SPMs were threshold at $p < 0.001$ (uncorrected) with a minimum cluster extent of $k \geq 5$ voxels. Results will report the peak voxel p value and the number of voxels (k).

To assess the size of the hippocampal sclerosis and surrounding cortex, volumetric measures of hippocampal, entorhinal, and parahippocampal gyrus were obtained for all participants with the Freesurfer image analysis suite (Fischl, 2012; Reuter et al., 2012), which is documented and freely available for download-ing online (http://surfer.nmr.mgh.harvard.edu/). Non-parametric tests (Kruskal–Wallis, SPSS 18.0) were used to compare these measures between the patient and controls groups. To control global differences, intracranial volume was included in the analysis as a covariate, which was not found to be significant. The percentage of reduction of each structure was calculated for each patient group in comparison to the control group and is reported in **Table 2**.

RESULTS

MAIN EFFECTS

A complete report of the results at threshold $p < 0.001$ (uncorrected) with a minimum cluster extent of $k \geq 5$ voxels can be seen in **Table 3**. All three groups of participants showed adaptation to lyrics in the left and right STG and STS that was however considerably more extended in Controls (2474 and 2423 voxels) than in LTLE (541 and 388 voxels) and RTLE patients (201 and 165 voxels). Between-group comparisons revealed significantly weaker adaptation effects in the LTLE but not in the RTLE as compared to Controls in the left STS (**Figure 1A**).

In all three groups, adaptation to melody was found in the left and right STG and STS, again more extended in Controls (2380 and 1830 voxels) than in LTLE (245 and 295 voxels) and RTLE patients (106 and 111 voxels), as well as in the cerebellum. The Control group showed, in addition, adaptation in the left PMC (52 voxels) that was not observed in patients (**Figure 1B**). However, between-group differences failed to reach significance.

INTERACTION EFFECTS

Interaction effects were calculated with the contrast $[(D_MS_L + S_MD_L) - (D_MD_L + S_MS_L)]$ and were taken to represent an integrated processing of lyrics and melodies in songs. Only the control group showed interaction effects at $p < 0.001$ $k \geq 5$, which were located in the bilateral posterior STG/STS (left: 169 voxels and right: 323 voxels). No such effect was observed in LTLE and RTLE patients. To visualize areas that simply may not have passed our statistical criterion, we inspected the data at a very lenient level of $p < 0.05$ uncorrected ($k > 5$). Controls showed an extended region within the left (1936 voxels) and right (2176 voxels) STG/STS (**Figure 2A**). At this threshold, RTLE patients showed a pattern that was similar to Controls, but considerably less extended (554 and 1501 voxels) (**Figure 2B**). Interestingly, LTLE patients showed nearly no interaction in the temporal lobe at this very lenient threshold (238 and 35 voxels) (**Figure 2C**). Indeed, between-group comparisons revealed a significantly weaker interaction effect in the LTLE than the Control group in the right STG (**Figure 1C**) whereas the difference between the RTLE patients and Controls did not reach significance. Details on interaction effects are shown in **Table 4**.

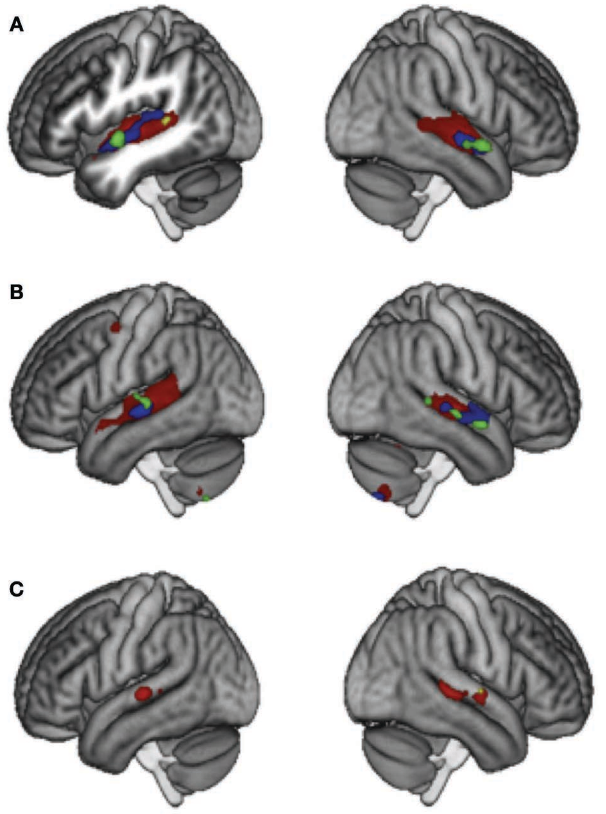

FIGURE 1 | Main effects of Adaptation to Lyrics (A) and Melody (B), and the Interaction (integration contrast) (C). Threshold $p < 0.001$ $k \geq 5$ uncorrected. Results for Control group (red), LTLE (blue), RTLE (green), and Controls vs. LTLE (yellow).

INDEPENDENCE EFFECTS

Greater adaptation to lyrics as compared to melody was found bilaterally in the anterior region of the STG (23 and 196 voxels) in the control group, suggesting an independent processing of lyrics in this region. Greater adaptation to melody as compared to lyrics was obtained bilaterally in the cerebellum in RTLE patients. However, between-group differences failed to reach significance (**Figure 2A**). Details on independence effects are shown in **Table 4**.

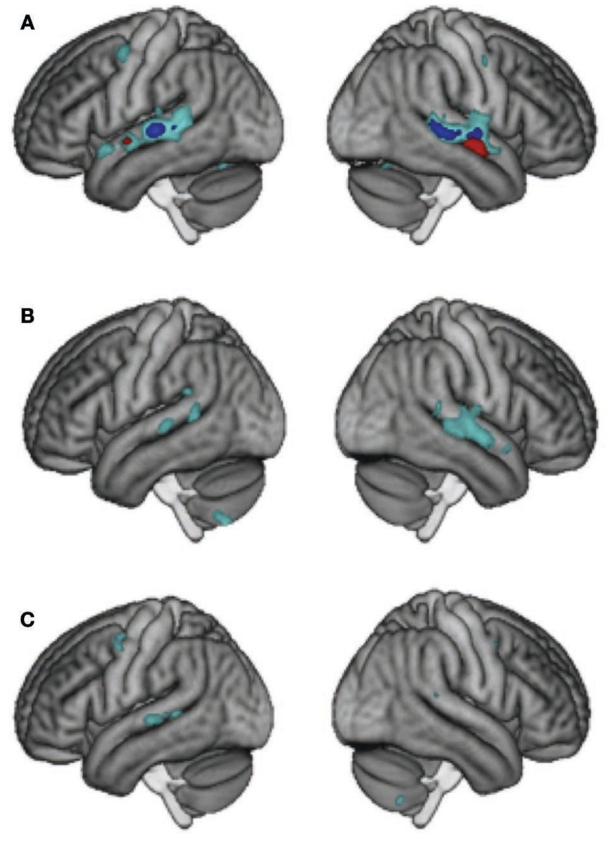

FIGURE 2 | "Gradient of integration" for (A) the Control group (B) RTLE and (C) LTLE patients. Specificity for lyrics is shown in red ($p < 0.001$ $k > 5$ uncorr.), interaction in dark blue ($p < 0.001$ $k > 5$ uncorr.) and weaker interaction in cyan (Interaction at $p < 0.05$ $k > 5$ uncorr.).

DISCUSSION

The aim of the current study was to assess the modulatory effects of a unilateral hippocampal lesion on the incidental emergence of a song memory trace and the integration of lyrics and melodies into a conjunctive representation. To this end, neural adaptation to song repetition – as a proxy for song memory formation – was examined in patients with left or right hippocampal sclerosis in comparison to healthy controls using an fMR-adaptation paradigm. It was hypothesized that damage to the hippocampus may disrupt feedback connections to the lateral temporal lobe and thus preclude the establishment and update of a sensory memory trace. As a consequence, damage to the hippocampus may result in weaker neural adaptation in the STG. In particular, hippocampal lesions could hinder the integration of lyrics and melodies into a unified memory trace (Diana et al., 2007; Staresina and Davachi, 2009; Graham et al., 2010; Shimamura, 2010).

The main findings of this study were indeed that the neural adaptation to lyrics repetition as well as the integration of lyrics and melodies in songs (as reflected by the statistical interaction between adaptation effects for lyrics and melodies) was reduced in patients with left hippocampal sclerosis. More specifically, the direct comparison of these patients with healthy control participants revealed a weaker adaptation to lyrics in the left STS and a weaker integration of lyrics and melodies in the right STG. If one accepts the notion that neural adaptation reflects the emergence of a memory trace (see Introduction), these results are in line with our hypotheses and previous work showing that left hippocampal damage may lead to weaker memory for lyrics (Samson and Zatorre, 1991) and may hinder the integration of lyrics and melodies into a unified memory representation (Samson and Zatorre, 1991; Sammler et al., 2010).

All three groups of participants showed adaptation to the repetition of lyrics or melodies in the bilateral STG and STS, but in both patient groups, these effects were markedly smaller in spatial extent when compared to healthy controls. Notably, patients with left (but not right) hippocampal sclerosis exhibited significantly decreased adaptation to lyrics in the left STS, which is known to play a role in phonemic processing and also known to be crucial for the perception of a sound as speech (Dehaene-Lambertz et al., 2005; Liebenthal, 2005; Möttönen et al., 2006; for a review on STS, see Hein and Knight, 2008). This finding is most likely tied to the role of the left medial temporal lobe in verbal processing (Meyer et al., 2005; Wagner et al., 2008; Greve et al., 2011) and may reflect the perturbed build-up of memory traces for lyrics (and verbal material in general) due to disrupted feedback connections between medial and lateral structures of the left temporal lobe (Eichenbaum, 2000). Such an interpretation could be supported by the verbal memory deficit documented in the LTLE patients of the present study (assessed with the RAVLT) and, although we did not collect behavioral data for this experiment, these results are also in agreement with the behavioral results of Samson and Zatorre (1991). That study showed that the recognition of sung lyrics after listening to unfamiliar songs was impaired in patients with left (but not right) medial temporal lobe lesions.

Although patients with right hippocampal sclerosis showed nominally reduced adaptation and integration effects, these did not significantly differ from those in healthy controls, suggesting rather normal song processing and lyrics–melody integration in these patients. While the latter is in line with previous behavioral data showing spared integration of lyrics and tunes after right anterior temporal lobe resection (Samson and Zatorre, 1991), our hypothesis on reduced adaptation to melodies was not confirmed. This may partly be due to the stimulus material used: even if melodies were repeated to induce adaptation, they differed in octave sung by sopranos, tenors, altos, and bass. Most likely, adaptation effects are not fully robust to transposition of melodies. Furthermore, adaptation to melodies was generally weaker than adaptation to lyrics, as attested by the results in healthy participants, possibly resulting in a floor effect. Our participants may have paid less attention to melodies than to lyrics (as the latter convey the message) leading to weak adaptation, given that a lack of attention reduces adaptation effects (Chee and Tan, 2007). Alternatively, several lines of evidence suggest that melodies may be processed more bilaterally than lyrics (Samson and Zatorre, 1992; Binder et al., 2000; Besson and Schön, 2003; Peretz and Coltheart, 2003; Schön et al., 2005; Patel, 2008; Koelsch, 2012), leading to less severe deficits in processing melodies than in verbal

Table 3 | Main effects of lyrics and melodies repetition for each group and comparison between Controls and LTLE.

Group	**Adaptation for lyrics**				**Adaptation for melody**			
	Area	**Size(*k*)**	***x, y, z* (mm)**	***Z***	**Area**	**Size(*k*)**	***x, y, z* (mm)**	***Z***
Control	Left hemisphere				Left hemisphere			
	STG/STS	2474	−58, −6, −6	5.75	STG/STS	2380	−64, −29, 3	5.12
			−62, −17, 0	5.52			−54, −39, 3	4.75
			−48, −39, 6	5.04			−66, −39, 12	4.68
	Temporal pole	11	−51, 9, −18	3.86	PrCG	52	−52, −5, 51	3.94
					Cerebellum	55	−26, −62, −55	3.75
	Right hemisphere				Right hemisphere			
	STG/STS	2423	62, −9, −6	5.59	STG/STS	1830	60, −17, −3	5.85
			60, −0, −13	4.76			46, −36, 2	4.26
			62, −24, 2	4.39			62, −0, −10	4.12
	Cerebellum	10	16, −80, −46	3.26	Cerebellum	148	34, −63, −58	3.91
					Cerebellum	27	30, −57, −27	3.59
LTLE	Left hemisphere				Left hemisphere			
	STG/STS	541	−58, −5, −9	4.60	STG	245	−57, −21, −3	4.68
			−56, −15, −3	4.05				
			−66, −33, 9	3.65				
	Right hemisphere				Right hemisphere			
	STG/STS	388	62, −9, −7	4.41	STG/STS	295	62, 2, −9	3.69
			62, 2, −13	3.85			57, −11, −9	3.67
							58, −5, −1	3.44
					STG/STS	92	54, −24, 0	3.69
					Cerebellum	134	26, −74, −60	3.67
RTLE	Left hemisphere				Left hemisphere			
	STG/STS	201	−63, −6, −6	4.26	STG/STS	106	−66, −26, 2	3.55
							−58, −18, 6	3.24
					Cerebellum	20	−24, −66, −60	3.30
	Right hemisphere				Right hemisphere			
	Temporal pole	165	62, 3, −10	4.13	STG/STS	61	62, −0, −12	3.95
	STG/STS		63, −9, −10	3.29	STG/STS	50	58, −17, −4	3.65
					STG/STS	21	69, −36, 3	3.41
Control vs. LTLE	Left hemisphere				Left hemisphere			
	STS	25	−46, −39, 6	3.60				

processing after unilateral temporal lobe damage. Further studies will be necessary to clarify this issue.

One novel finding is the main effect of melodies in the cerebellum in all groups (without group differences). Since activity in the cerebellum has been frequently reported in other studies using sung material (Parsons, 2001; Callan et al., 2007; Lebrun-Guillaud et al., 2008; Tillmann et al., 2008; Merrill et al., 2012), these effects may be linked to optimization of the fine sensory acquisition and internalization of input–output characteristics of stimuli, a process related to the creation of internal models of vocal articulation (Parsons, 2001; Callan et al., 2007; Stoodley and Schmahmann, 2009), that may function independently from the hippocampus.

As previously reported (Sammler et al., 2010), healthy participants presented maximum integration of lyrics and melodies in the posterior STS with a continuous decay of the lyrics–melodies integration along the posterior–anterior axis, toward regions of independent processing of lyrics in the anterior STG. These effects were shown bilaterally in the present experiment, expanding the previously reported effect, which was restricted to the left hemisphere. This analysis illustrates a "gradient of integration" from more to less integrated processing. In line with the literature on music and language (Scott et al., 2000; Davis and Johnsrude, 2003; Scott and Johnsrude, 2003; Friederici, 2011; Gow, 2012), this gradient poses an integrative processing of songs at the prelexical and phonemic level in the mid-STS. Consequently, information can be transmitted both along an anterior pathway to the temporal pole for an independent analysis of the linguistic content, and along a posterior pathway to the left PMC for the integrated sensori-motor conversion of the stimuli. In other words, lyrics and melodies might split up in the ventral pathway for semantics and comprehension (Griffiths, 2001; Patterson et al., 2002; Hickok and Poeppel, 2007; Saur et al., 2008; Friederici, 2009, 2011; Hickok et al., 2011) but stay integrated in sensori-motor dorsal pathways (Kiebel et al., 2008; Loui et al., 2009).

Table 4 | Integration and independence for each group and between controls and LTLE.

Group	Area	Size (*k*)	*x, y, z* (mm)	*Z*
INTEGRATION				
Control	Left hemisphere			
	STG	164	−63, −23, 2	4.39
	MTG	5	−63, −36, 3	3.18
	Right hemisphere			
	STG	235	56, −32, 0	3.98
			51, −38, 5	3.65
	STG	82	66, −11, −3	3.76
	STG	6	66, −20, 0	3.18
Control vs. LTLE	Right hemisphere			
	STG	6	63, −9, 0	3.19
LYRICS INDEPENDENCE				
Control	Left hemisphere			
	STG	15	−63, −5, −6	3.29
	STG	8	−46, −41, 8	3.32
	Right hemisphere			
	STG	196	63, −6, −15	3.79
MELODY INDEPENDENCE				
LTLE	Left hemisphere			
	Cerebellum	10	−18, −66, −61	3.58
RTLE	Left hemisphere			
	Cerebellum	19	−12, −83, −46	3.77
	Cerebellum	6	−24, −66, −61	3.21
	Right hemisphere			
	Cerebellum	18	14, −81, −46	3.62

Contrary to healthy participants, both patient groups showed very weak levels of lyrics–melody integration in the bilateral mid-STG/STS, and only after lowering the statistical threshold to $p < 0.05$ (uncorrected). This effect may reside on generally weaker adaptation effects in both patient groups. The spatial extent of this weak lyrics–melody interaction was particularly small in patients with left hippocampal sclerosis who also showed a significantly reduced interaction effect in the right STG as compared to controls. These tendencies suggest a partial (although not complete) disruption of integrated processing in clinical populations and indicate that the conjunctive representation of lyrics and melodies depends on intact medial temporal lobe structures, particularly in the left hemisphere. Overall, this finding is in line with previous studies in patients with anterior temporal lobe resection including parts of the hippocampus (Samson and Zatorre, 1991). These experiments showed a perturbed integration of verbal and melodic song components in patients with left (but not right) temporal lobe resections, i.e., a selective deficit in recognizing lyrics that was independent from recognition memory for melodies. It is worth to mention that in both the present and previous studies, the integration deficit may reside on a more general deficit to process lyrics, as supported by the weaker adaptation for lyrics and reduced performance in neuropsychological tests on verbal memory in our patients with left hippocampal sclerosis.

Taken together, adaptation to lyrics and integration of lyrics and melodies within songs appear to be less efficient in patients with left hippocampal damage as compared to healthy controls. We propose that these lesions may hinder the build-up of a sensory memory trace for lyrics (with rather preserved mechanisms for melodies), which in turn might be at the origin of the reduced integration of lyrics and melody. These combined effects could be attributed to hippocampal malfunction *per se* or to a more global disconnection of lateral temporal neocortical structures caused by repetitive seizures or epilepsy history (Yasuda et al., 2010; Besson et al., 2012), both of which can disrupt the hippocampal top-down modulatory influence on STG/STS. If this is the case, it is possible that adaptation could also be reduced for stimuli other than lyrics, melodies, or songs, demonstrating a more general adaptation and putative encoding deficit following disruption of cortico-hippocampal processing loops.

Interestingly, an independent analysis of the connectivity profiles in our patients showed asymmetries between the left and right hemispheric lesion groups: LTLE patients exhibited more extended and more strongly left-lateralized disconnections, as opposed to more discrete and bilateral connectivity deficits in RTLE (Besson et al., 2012). Such differences in connectivity profiles provide an additional explanation for the nominally stronger impairments in patients with left hippocampal sclerosis as compared to patients with right hippocampal sclerosis. In sum, the present data indicate that an imbalance in the left hippocampo-cortical system, due to hippocampal sclerosis and/or disrupted connectivity with STG/STS, affects the incidental emergence of a memory trace of verbal song components and precludes the build-up of a conjunctive representation that integrates lyrics and melodies.

CONCLUSION

To the best of our knowledge, this is the first study to investigate the processing of songs using fMRI in patients with unilateral hippocampal sclerosis. We showed that the adaptation to lyrics and the integration of lyrics and melodies was diminished in lateral temporal lobe regions in patients with left hippocampal sclerosis while a similar but non-significant result pattern was found in patients with right hippocampal sclerosis. These findings suggest the importance of hippocampal top-down modulations on the STG/STS during repetitive exposure to songs. We interpret the observed adaptation patterns to be a result of a disturbed connectivity in a hippocampal–cortical network, weakening the emergence of a memory trace for lyrics and the integrated processing of songs as a unified percept. Overall, these data provide a novel contribution by suggesting that the integration shown in healthy participants is tied to the integrity of the medial temporal lobe and its connections with the lateral temporal cortex.

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Chapter 6: Neural correlates of binding lyrics and melodies for the encoding of new songs.

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Abstract

Songs naturally bind lyrics and melody into a unified representation. Using a subsequent memory paradigm, we examined the neural processes associated with binding lyrics and melodies during song encoding. Participants were presented with songs in two conditions: a unified condition (melodies sung with lyrics), and a separate condition (melodies sung with the syllable “la”). In both cases, written lyrics were displayed and participants were instructed to memorize them by repeating them covertly or by generating mental images of the songs. We expected the unified condition to recruit the posterior superior temporal gyrus, known to be involved in perceptual integration of songs, as well as the left inferior frontal gyrus (IFG), which has an important role for the binding of verbal information. Conversely, we hypothesized that the separate condition would engage a larger network including the hippocampus to bind lyrics and melodies of songs, and the basal ganglia and the cerebellum to ensure the correct sequence coupling of verbal and musical information in time. Binding lyrics and melodies in the unified condition revealed activation of the left IFG, bilateral middle temporal gyrus (MTG), and left motor cortex, suggesting a strong linguistic processing for this condition. Binding in the separate compared to the unified condition revealed greater activity in the right hippocampus as well as other areas including the left caudate, left cerebellum, and right IFG. This study provides novel evidence for the role of the right hippocampus in binding lyrics and melodies in songs. Results are discussed in light of studies of binding in the visual domain and highlight the role of regions involved in timing and synchronization such as the basal ganglia and the cerebellum.

Keywords: binding, lyrics, melodies, songs, hippocampus, basal ganglia, IFG

Introduction

Although enjoyable, widespread, and seemingly effortless, learning and remembering songs entail high-level cognitive processes that require the binding of verbal and musical information into a unified representation. Neuroimaging studies of song perception have led to enlightening debates on the independence or interaction of music and language networks (Schön et al., 2005). Two studies have suggested the involvement of the posterior areas of the superior temporal gyrus (STG) and superior temporal sulcus (STS) in the integration of lyrics and melodies within songs (Schön et al., 2010; Sammler et al., 2010). Despite these few studies that investigated the perceptual integration of verbal and musical information within songs, the neural mechanisms supporting the binding of lyrics and melodies in memory have received relatively less attention. To further explore this issue, we examined the cerebral structures underlying the binding of lyrics and melodies during encoding of new songs.

One widely used approach to study successful memory formation has been the subsequent memory paradigm (Wagner et al., 1998; Kim, 2011; Paller and Wagner, 2002). This paradigm allows identifying brain activity during encoding that can predict later success in recognition by comparing subsequently recognized trials with subsequently forgotten trials, known as the subsequent memory effect (SME). Such a paradigm has been instrumental in revealing the distinct contributions of regions in the medial temporal lobe (MTL) to memory (Davachi et al 2003; Staresina and Davachi (2006, 2009; Staresina et al., 2011). One recent study used the subsequent memory paradigm to examine the binding of visual objects features (i.e. shape and colors) in memory (Staresina and Davachi, 2009). In one condition, objects images were presented with a color in a unified manner. In two other conditions, gray-scale objects and color were presented separately. The object in gray-scale was presented with a color frame displayed either simultaneously with the object (spatial discontinuity condition) or with a short delay (spatial-temporal discontinuity condition). In these discontinuity conditions, participants were instructed to use imagery to bind these features into a unified representation. Interestingly, the magnitude of the SME in the hippocampus, unlike the neighboring perirhinal cortex, increased as function of the spatiotemporal discontinuity of the presented object and color representations.

To further explore the role of the hippocampus in memory binding, we developed a new paradigm involving auditory information. In this case, participants were required to bind lyrics with their associated melodies during song encoding. Hence, the present study aims at exploring the underlying brain mechanisms that support the binding of lyrics and melodies within songs. We examined subsequent memory for songs under two encoding conditions inspired by Staresina and Davachi's study (2009): 1) following a unified presentation of song components (sung lyrics) and 2) following a separate presentation of song components (simultaneous presentation of sung melody on the syllable "la" and of written lyrics). In both conditions, participants were asked to covertly and repeatedly sing the resulting song until the next trial and to retain the song for a recognition test. Critically, these two conditions are inherently different in terms of the cognitive effort of the participant. The unified presentation is a perceptually richer condition that already provides an integrated signal while the separate condition requires the participant to actively create a mental representation of the song.

Taking in consideration memory models describing the MTL binding function (Davachi, 2006; Diana et al., 2007; Ranganath, 2010) as well as recent empirical findings in the visual domain (Staresina et al., 2009), we suggest that the hippocampus may be required to integrate various elements of a song into a unified memory trace. Based on results reported by Staresina and colleagues (2009), we suggest that the involvement of the hippocampus during encoding of songs will enhanced when melody and lyrics are presented separately rather than in a unified presentation (sung lyrics), the hippocampus being particularly important to actively integrate separate components of an event.

Alternatively, the unified presentation of song lyrics might involve cerebral structures related to verbal binding. Given that verbal comprehension and memory for sentences may strongly rely on semantic and syntactic integration of word sequences, the unified condition can be considered as a form of binding, specific to the verbal domain (for a review see Opitz, 2010). To this regard, such a verbal binding has been shown to be supported by the left IFG (Hagoort, 2005; Opitz and Friederici, 2003). Although the integration of linguistic content embedded in a melody has not been studied, activation in the left IFG has been observed during musical imitation and vocal learning in singing (Brown et al., 2004). Thus, the left IFG may support the mnemonic binding of sung lyrics, particularly following the covert rehearsal imitating a given song.

As previously discussed, binding is required to integrate information both across space and time (Eichenbaum, 2013). It is therefore worth noting that these dimensions might interact differently in the visual and the auditory domains. On one hand, vision is largely governed by space, requiring rapid binding of synchronous events (Engel et al., 1997). On the other hand, audition is constrained by time variations (Sanders et al., 2011; Kiebel et al., 2008; Demany et al., 2010) and consequently requires precise timing and binding of unfolding sequences. Thus, the evoked binding network cooperating with the hippocampus may vary according to spatial and temporal demands of the task. In particular, the cerebellum and the basal ganglia, which are highly interconnected (Bostan et al., 2013), might be critical for binding auditory information. A non-motor role of the basal ganglia on speech perception has been previously proposed (for a review see Kotz et al., 2009; Kotz and Schwartze, 2010), and cerebellum activations have been frequently found during song perception and production (for a review see Callan et al., 2007). From a more general perspective both the cerebellum and basal ganglia have been shown to be crucial for sequence learning (Graybiel et al., 1994; Kotz et al., 2009; Shin and Ivry, 2003), and for generating temporal (Cope et al., 2014; Penhune et al., 1998; Schwartze and Kotz, 2013; for a review see Schwartze et al., 2012) and harmonic expectations (Seger et al., 2013). It is possible that activation of the cerebellum and basal ganglia may allow temporal coupling of syllables with musical notes during covert rehearsal, enhancing learning of the song sequence through auditory-motor binding. This idea is supported by studies reporting striatal contributions to auditory-motor binding in other not-singing tasks such as synchronized tapping to sounds (Hove et al., 2013). For instance, Schmitz and colleagues (2013) have shown functional connectivity between STG and basal ganglia in an auditory-motor binding task. By presenting sounds that were congruent or not with a human avatar breaststroke, the participants were asked to judge small perceptual differences in velocity in the scanner. The STG and STS showed greater activation for sound-movement bound representations. In line with the suggested temporal coupling role, the basal ganglia and the cerebellum showed greater functional connectivity with the STG when the sounds were congruent to the movement with which they were integrated. This supports that the basal ganglia and cerebellum may be crucial for sensory-motor binding to couple unfolding sound with other distinct elements. Consequently, we hypothesized that basal ganglia and cerebellum as well as the hippocampus may play an important role in binding lyrics and melodies through covert rehearsal.

In sum, the present study investigated the cerebral network involved in memory binding of songs in two different conditions, where lyrics and melodies were presented either in a unified, or in a separate way. Given the involvement of the posterior areas of the STG/STS in the processing of integrated song representations and the left IFG in binding verbal information and vocal imitation, we predicted that these regions would show a SME in the unified condition. Based on memory models of binding, we hypothesized the hippocampus would be more involved in binding resulting in greater SME in the separate than in the unified condition in this region. Furthermore, the separate condition may require higher temporal and mental imagery processing demands to allow the coupling of lyrics and melodies in time. Hence, we predicted a SME in the basal ganglia and the cerebellum in the separate condition.

Methods

Participants

Twenty-two healthy native French speakers participated in this study. They were all right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971), and reported to have normal hearing. All participants were non-musicians and musical experience was assessed by the Music Expertise Questionnaire (Ehrlé, 1998), indicating that participants were not music experts (mean score ±SD: 5.45± 2.79; max score: 27 points).

Participants were included after a screening phase to verify that they were all able to sing and imagine songs. General auditory imagery was measured with the Bucknell Auditory Imagery Scale (Zatorre et al., 2010), confirming that participants had normal auditory imagery abilities (Vividness scale mean: 5.34 ± 0.68; Control scale mean: 5.62 ± 0.66). To test the specific imagery of songs during the screening phase, participants listened to six songs and had to repeat them aloud and provide a subjective response on their ability to covertly rehearse each of them. Similarly, participants were also presented six melodies sung with the syllable “la” and accompanied by written lyrics. They were asked to sing aloud the correspondent songs and provide a subjective rating on their ability to imagine each song. To further ensure that participants were able to imagine a song by combining a melody with some written lyrics correctly, we developed a song plausibility test. In this test, participants were presented with 24 melodies and 24 written lyrics, where half of the resulting songs had a one-to-one mapping between the number of syllables in the lyric and the number of sounds in the melody, and half did not. Participants had to imagine the song and respond if the combination of melody and lyrics was plausible or not. After the screening of 37 volunteers, 13 participants were excluded because they did not achieve an accuracy score over 66 % in this test. Additionally, two females randomly selected among those with lower plausibility scores (67%) were excluded for gender counterbalance proposes, resulting in the final inclusion of 22 participants (11 female; years ±SD: 24.09 ±5.45; years of education ± SD: 16±1.69; mean song plausibility accuracy ± SD; 74% ± 0.05) in the MRI study.

The local ethics committee has approved this study and all participants provided signed written informed consent beforehand.

Stimuli

Two sets of 54 pairs of songs with interchangeable lyrics and melodies were specifically created based on a collection of 19^{th} Century French folk songs (Robine 1974). Syllables were matched to musical notes in a one-to-one basis. Each lyric consisted of 6 to 9 pronounced syllables and each melody consisted of 6 to 9 notes. The resulting songs had a variable duration between 2.5 to 3 seconds. One set of 54 pairs of songs was composed of *original* songs. The other set of 54 pairs of songs was created by recombining the lyrics from one song of the *original* pair with the melody from the other song of the *original* pair and vice versa (*rearranged* songs). By following this procedure, the level of familiarity for lyrics and melodies remained equivalent for the *original* and *rearranged* songs. Melodies of each *original* song were either sung with lyrics or sung using the syllable “la”. Melodies of each *rearranged* song used for recognition were sung with lyrics. The same female professional pop singer recorded all singing stimuli. Additionally, written lyrics were used during encoding.

Procedure

Before entering the scanner, participants received a short song imagery warm-up session based on the plausibility test previously described. Scanning was divided into six sessions to allow pauses every 10 minutes (without leaving the scanner or moving). Each session included 3 blocks, for a total acquisition of 18 blocks (Fig. 1). Each block included an encoding phase followed by an immediate recognition phase (Fig. 2).

The encoding phase included 6 encoding trials consisting of *original* songs and 2 baseline trials presented in random order. Following the presentation of each *original* song, a fixation-cross was displayed for a period of 6 seconds. During that period, participants were asked to rehearse the song by singing covertly and repeatedly until the next trial. In baseline trials, participants were prompted with a written number presented with white noise for 6 seconds, to control for visual and auditory stimulation relative to encoding trials. Following the stimulus presentation, a fixation-cross appeared in the screen and remained for a period of 6 seconds, and participants were asked to count down covertly from the displayed number until the next trial. Thus, the inter-stimulus interval was 12 seconds varying with a jitter of ±1 s that was naturally provided by the difference in length of songs to allow for fitting of HRF. The total duration of an encoding phase was 1 min 36 s. At the end of the encoding phase, a slide was displayed for 7 s to make the transition to the recognition phase.

The recognition phase consisted of 6 *original* songs and 6 *rearranged* songs, all of which were presented in random order. No visual cue was provided for the lyrics during recognition. After the presentation of each song, participants were asked whether the lyric had been previously sung with the presented melody or not, using a confidence rating scale. Participants had 3 seconds to press one of four buttons: “No, sure”, “No, not sure”, “Yes, not sure”, “Yes, sure”. Each recognition phase took 1 min 24 s.

Blocks were randomly assigned to two different encoding conditions. In the unified condition, *original* songs were presented in a unified manner (sung lyrics. In the separate condition, the melody of the *original* songs was sung using the syllable “la” in place of lyrics and the lyrics were presented visually. In both conditions, auditory stimuli were presented twice to facilitate encoding while written lyrics were simultaneously displayed in the screen. The assignment of songs to either the unified or separate condition was counterbalanced across participants so that all songs were used in both conditions. Blocks from each condition were presented in an interleaved fashion and the order of the blocks was counterbalanced across participants.

The total duration of the functional acquisition was approximately 54 min ± 5 s depending on the length of the brief pauses between sessions.

fMRI parameters

Functional magnetic resonance imaging (fMRI) was performed on a 3T Siemens TRIO scanner (Siemens) at the Centre de Neuroimagerie de Recherche at the Pitié-Salpêtrière Hospital in Paris. Before the functional scans, high-resolution T1-weighted images (1 x 1 x 1 mm voxel size) were acquired for anatomical coregistration using a magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence (TR= 2300 ms, TE=4.18 ms).

Six series of 264 volumes of oxygenation level-dependent (BOLD) images were obtained using a single-shot echo-planar gradient-echo (EPI) pulse sequence (TR= 2100 ms, TE= 29ms, the first four volumes were later discarded to allow for T1 saturation). Forty slices were acquired perpendicular to the hippocampal plane (voxel size 3 mm isotropic, with a slice gap of 0.3 mm) with a field of view of 204 x 204 mm, and a flip angle of 90º. Additionally seven series of 8 volumes (the first four volumes were later discarded to allow for T1 saturation) were acquired with the same parameters except the phase encoding, which was set in the opposite direction. Those extra series were only used for the deformation field correction proposes as described in Anderson and colleagues (2003) and Smith and colleagues (2004). Auditory stimulation was delivered though MR Confon headphones and participants wore earplugs to minimize the scanner noise during stimulus presentation and imagery.

Behavioral analyses

Behavioral data from the recognition phases were analyzed in PASW statistics v18.0 and used for two different purposes: 1) provide an overall measure of recognition success, and 2) provide an individual success score for each encoded item which was later related to fMRI data during encoding. First, recognition responses were analyzed using receiver operating curves, by calculating the Areas Under the Curve (AUC) for the unified and the separate encoding conditions, which took into account both accuracy and confidence ratings.

Individual memory scores of each encoding trial were calculated using recognition accuracy for both the *original* and *rearranged* for each song and incorporated both accuracy and confidence responses. A score of 0.5 was given to each *original* or *rearranged* song that was correctly recognized or correctly rejected with high confidence, and 0.25 for low-confident correct scores. Furthermore, for each missed *original* song or false alarm, the item was penalized with a score of -0.5 for high-confident responses, or -0.25 for low-confident responses. Thus, the maximum memory score possible was 1, the sum of 0.5 from a high-confident hit of the *original* song and 0.5 from a high-confident rejection of the *rearranged* song (see Table 1.a.). Trials with a memory score of zero or below were considered unsuccessful or at chance and were transformed to zero, since negative memory scores were not expected to modulate brain activity.

These scores were used for subsequent memory analysis in two ways. For the GLM model, scores were used to tease apart successful (hits) and unsuccessful (misses) trials building separate regressors for SPM analysis. Only trials with both successful recognition of the *original* songs and rejection of the *rearranged* songs were considered successful. Trials with a score of 0.25, corresponding to a high-confident correct answer (+0.5) and a low-confident incorrect answer (-0.25) were left out of the analysis, since they may reflect familiarity processes that are difficult to interpret within the limits of the current design (see Table 1.b.).

Memory scores (ranging from 0 to 1) were also entered as a parametric modulator of encoding, representing a putative sign of binding success. The parametric analysis of fMRI data assumes a gradation in activation of brain areas involved in binding which may be modulated not only by accuracy, but also by the degree of confidence in these two responses, which might reflect memory strength of the encoded item. In this way, when responses for both *original* and *rearranged* songs are both correct and confident, the studied song may have been better encoded, with greater detail, than when the participant was not sure (see Table 1.b.).

fMRI GLM analysis

All fMRI analyses were computed using SPM8 (Wellcome Trust Centre for Neuroimaging). Preprocessing of functional images included spatial realigment and corregistration of the functional and anatomical data. Then, images were distortion corrected and normalized to the MNI space and smoothed using a 3D Gaussian kernel of 8 mm full-with at half maximum (FWHM). In the first level, the analysis was carried within a normalized grey matter mask based on the normalized mean anatomical image.

Data was modeled and estimated using the GLM to compare successful versus unsuccessful encoding trials. For the GLM, trials were binned by condition as well as encoding success (success sorting described in the previous section) to create four different regressors (unified-successful, unified-unsuccessful, separate-successful; separate-unsuccessful) Additionally, two regressors were also created for the baseline encoding trials and all recognition trials. Initially, stimuli presentation and imagery periods were modeled separately at the first level (within-subjects level) and then combined at the second level (between-subjects level) to form encoding trials.

First, we looked at task effects using a factorial design with one factor (encoding) and looking at the positive effect of encoding reflected by a t contrast. Additionally, we used one-sample t-tests to compare activity during successful trials only to the baseline condition, together with one-sample t-tests of successful trials in each condition against baseline. General activation on the separate and unified conditions, irrespective of memory performance was compared using one-sample t-tests. Second, we looked at SMEs comparing successful against unsuccessful trials using one-sample t-tests in each condition.

fMRI parametric analysis

High confidence during recognition of *original* and *rearranged* is an emergent property of recollection processes (see Diana and Ranganath, 2011), such that greater degree of confidence in both responses reflects stronger recollection. The hippocampus has been shown to be particularly sensitive to recollection of item and context associations (Diana et al., 2007), consistently with the binding role of the hippocampus previously described. Therefore, to look at the combined effect of confidence and accuracy on subsequent memory, we carried out a parametric modulation analysis. We examined the extent to which BOLD activation was modulated by memory performance, using the memory scores for each encoding trial previously described (see Table 1.b.). Then, one sample t-tests were used at the group level to evaluate SME for each encoding condition (unified and separate) and for the contrast between conditions (separate > unified, and unified > separate).

Correlation between BOLD activation and memory performance

Additionally, to explore the relationship between neural changes and behavior within our a priori regions of interest (ROIs), brain activation results from the parametric analysis from each condition were correlated with memory performance across participants. The ROI analysis allows a more sensitive exploration of relevant areas controlling for Type I error (Poldrack, 2007). We used the Automatemed Anatomic Labeling (AAL) atlas (Tzourio-

Mazoyer et al., 2002) to define neuroanatomical ROIs including subregions within the medial temporal lobe (hippocampus, parahippocampal gyrus), basal ganglia (caudate, pallidum, and putamen) and IFG (orbital part, triangular part, and opercular part).

Beta values from the parametric analysis for the separate and the unified conditions respectively were extracted within each ROI using the MarsBar toolbox (Brett et al., 2002) and were used as a neural measure of encoding. Beta values were then correlated to recognition performance, reflected by each subject's AUC for each condition. Note that both neural and behavioral measures here are sensitive to accuracy and confidence in a similar manner, being therefore suitable correlates. We included all participants in this analysis, with the prediction that participants that did not perform above chance would exhibit lower activation in the predicted areas compared to successful participants. Of note, unlike statistical parametric maps, this analysis illustrates individual differences across participants, with the prediction that participants with greater activation on the ROIs would also show more accurate recognition, incurring in greater successful binding overall.

Results

a) Behavior

Recognition memory performance was measured using the AUC for each encoding condition, thus taking accuracy and confidence into account. All participants recognized songs above chance in the unified condition ($p < 0.05$). This suggests that participants could successfully bind lyrics and melodies and that they followed the instructions. In the separate condition, 7 participants did not surpass this threshold and were thus excluded from the SPM analysis. The statistic results of the AUC for each participant in both conditions are reported in Table 2.

b) fMRI GLM analysis

All SPMs were threshold at $p < 0.001$ (uncorrected) with a minimum cluster extent of 5 voxels (see Table 3). Anatomical location of significant clusters was carried out based on the Automed Anatomic Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002).

Task effects

A comparison of all encoding trials against the baseline trials revealed significant activation in bilateral STG, middle temporal gyrus (MTG), left IFG, right caudate, left putamen and several regions of the cerebellum (see Fig. 3A). Full list of regions activated by the task is reported in Table 3. A comparison of unified against separate condition revealed significantly greater activation in bilateral STG, bilateral MTG as well as orbital part of the left IFG and right anterior cingulum (see Fig. 3B).

Restricting this analysis to successful trials only against the baseline trials, additional activation was found in the right and left hippocampus, as well as extended clusters in the right IFG and right caudate. When looking at successful trials against baseline within each condition, the separate condition also revealed both right and left hippocampus, together clusters in right and left caudate. Conversely, for the unified condition, we found activation in bilateral caudate left putamen and the left hippocampus.

Subsequent memory effects

Activation related to the subsequent memory effect (SME) for the binding of lyrics and melodies was assessed comparing successful with unsuccessful trials in each condition. SME in the unified condition revealed a cluster in the left IFG together with activation in bilateral MTG and the left postcentral gyrus (Fig. 4A). Conversely, SME during the separate condition revealed significant activation in the right hippocampus, left caudate, the orbital part of the right IFG, right superior frontal gyrus, left middle frontal gyrus, MTG and bilateral cerebellum (Fig. 4B). A full list of regions and *p* values is reported in Table 4.

c) fMRI parametric analysis

To look at SME as a function of both accuracy and confidence, we carried out a parametric modulation analysis. Parametric modulation results were also threshold at $p < 0.001$ (uncorrected) with a minimum cluster extent of 5 voxels. Results for the separate condition, unified condition, the comparison between separate and unified conditions and vice versa are fully reported in Table 5.

In the unified condition, SMEs were shown in areas within the left hemisphere, including the left MTG, the left IFG and the left postcentral gyrus (see Fig. 5A). In the separate condition, SMEs revealed the engagement a greater number of regions as described in Table 5 (see Fig. 5B).

No differences were observed when comparing the unified against the separate condition. However, the comparison of the separate against the unified condition revealed significant modulation of activity with memory scores in various regions. In the left hemisphere, few clusters of activations were found in the MTG, the insula and the anterior cingulum. In the right hemisphere, activations were found in the hippocampus and the IFG, together with a cluster in the fusiform gyrus, and few cerebellum activations in the left IV-V, left Vermis IV-V and right vermis III (see Fig. 5C).

d) Correlation between BOLD activation and memory performance

Beta values from the parametric analysis were averaged within each anatomically defined ROIs and correlated with memory performance for each condition. In the unified condition, positive correlations were found for the left IFG (opercular and triangualar parts). In the separate condition, positive correlations were found in the right hippocampus (see Fig. 6), and the right parahippocampal cortex within the MTL, the right putamen, right pallidum and left caudate within the basal ganglia and both right (opercular and triangular part) and left (orbital part) IFG. The full list of significant Pearson correlations (one-tailed, $p < 0.05$) and p values is reported in Table 6.

Discussion

The present study aimed at examining the neural substrates underlying the binding of lyrics and melodies during encoding of songs. Two different encoding conditions for the binding of lyrics and melodies were manipulated. In the unified condition, participants listened to melodies sung with lyrics while viewing written lyrics and were asked to mentally rehearse and maintain the song. In the separate condition, participants listened to melodies sung on the syllable “la” while viewing written lyrics, requiring participants to mentally combine these two separate information into a song. Binding was addressed by asking participants to recognize the correct melodic context for the lyrics corresponding to the *original* song among other *rearranged* songs. It is worth noting that *rearranged* songs where created with the same lyrics and melodies of the *original* songs but combined in a wrong match, and thus subsequent recognition memory could only rely on the correct binding of the two elements.

Behavioral results

Behavioral analysis using receiving operating curves revealed that all 22 participants recognized songs in the unified condition, whereas only 15 participants were able to recognize songs above chance in the separate condition. This indicates that the additional cognitive effort required for binding under the separate encoding condition trades off with memory performance when compared to the unified condition. Although the song plausibility test, performed prior to the experiment, confirmed that all participants were able to correctly imagine a song by combining a melody with some written lyrics, this behavioral result suggests that the separate condition may have been more difficult than the unified condition. On the one hand perceptual similarity between encoding and retrieval that was higher in the unified than in the separate condition may have facilitate the task. On the other hand, the manipulation of lyrics and melodies to form an integrated representation in the separate presentation adds an additional process for song encoding, which may be behind this behavioral result. Thus, it is complicated to dissociate the effects of difficulty from the proper differences on the nature of binding itself. Only participants with above chance performance in both conditions were therefore included for neuroimaging analysis. Therefore, although the number of subsequently recognized and forgotten trials may differ between conditions, the SME resulting from the comparison of trials within condition should not be contaminated by difficulty factors. However, our experimental design cannot exclude the interference of difficulty on comparison between conditions. Consequently, neuroimaging results are interpreted carefully in regard to the literature.

Task general activation

During the encoding phase, participants were asked to imagine songs after being exposed to lyrics and melodies in two different conditions. Thus, general task activations irrespective of memory performance should reflect a covert singing network. Brain activity during the task was shown in bilateral cortical regions in the IFG, medial frontal gyrus (MFG), superior frontal gyrus, STG, MTG, the temporal pole, the SMA, the left IPL, left supramarginal gyrus areas VI, VIIb and VIII within the cerebellum bilaterally, and subcortical activations in the right caudate and left putamen. These activations are consistent with an extended covert singing network, in line with previous studies on covert singing (Langheim et al., 2002; Callan et al., 2006). Since this contrast merges activation from subsequently recognized and forgotten trials, it is not surprising that no MTL activation was shown.

However, focusing on successful trials only as compared to baseline trials, additional activations were also found in bilateral hippocampi, as well as the right IFG and right caudate, suggesting the involvement of those structures in encoding. When we limited this comparison to the separate condition only, bilateral activation was found in the hippocampus and the caudate. However, on the unified condition the comparison of subsequent successful encoding trials against baseline only revealed significant activation in the left hippocampus, and not the right. The lateralization of this activation profile is in line with previous results (Alonso et al., 2014), which have shown the detrimental effect of a left hippocampal lesion on the integration of lyrics and melodies during listening to songs presented in a unified manner. The current results provide novel evidence suggesting the particular cooperation of a covert singing network with the hippocampus and caudate during a song encoding task.

Binding of lyrics and melodies in unified condition

In line with our hypothesis, SME in the unified condition, as assessed by the GLM analysis, revealed activations in the bilateral MTG, the left postcentral gyrus and the parts triangularis of the left IFG, suggesting the involvement of an auditory-articulatory network. The parametric analysis incorporated confidence ratings with accuracy measures to look at modulations of brain activity, becoming more sensitive to recollection. The parametric analysis showed modulations of activity in relation to SME in similar regions to the GLM in the left hemisphere. Since encoding required the covert rehearsal of songs, it is not surprising that this kind of binding prompts the phonological loop (Buchsbaum and d'Esposito, 2008; Buchsbaum, 2013). Given that songs under the unified condition already provided an integrated percept to be covertly repeated, it is possible that this condition may have strongly relied on the phonological loop for encoding. This interpretation is coherent with previous data showing left IFG activation in relation to articulatory learning (Rauschecker et al., 2008).

To look at the particular involvement of the ROIs, correlation of brain activity with memory performance across subjects was calculated within the different regions. The results highlight the implication of the left IFG in binding for the unified condition. These results are in agreement with the binding role of Broca's area for language processing suggested by previous studies (Hagoort, 2005), and further extends the role of this area in the particular case of lyrics and melody integration. Taking into account the strong evolutionary impact of language, it may be the case that a specialized region, such as Broca's area, may process binding involving verbal (syntactic and articulatory) information. Our results accentuate the role of IFG and MTG on imagery and encoding of new songs, in line with previous findings on familiar songs (Herholz et al., 2012). However, future studies are needed to address if other non-verbal auditory binding examples, such as for instance timbre and melody, may depend on a similar mechanisms, or whether it is restricted to verbal binding.

Binding of lyrics and melodies in separate condition

Different activations were obtained when lyrics and melodies were presented in the separate condition. In line with our hypothesis, results from the GLM revealed active clusters in the right hippocampus, left caudate, and the cerebellum bilaterally (left area IX; right area III; Vermis III), as well as in other regions including the right IFG, right superior frontal gyrus (SFG), left middle frontal gyrus (MFG) and left MTG. However, in contrast with the GLM, the parametric analysis showed a slightly different network, suggesting that confidence nuances on accuracy that could be related to recollection processes might be particularly relevant to understand binding on the separate condition. The parametric analysis coincided with the GLM on the implication of the left MTG, left caudate and Vermis III.

This parametric analysis showed modulations of activity in relation to SME in the right caudate, SFG bilaterally, left MFG, a small region in the left IPL and some additional cerebellum areas, including area IV-V in the left hemisphere and areas II and X in the right hemisphere. Taken together, the results of the GLM and the parametric analysis highlight the implication of the basal ganglia, specially the left caudate, and the cerebellum bilaterally, in line with our predictions and suggesting a main implication of a sequencing and timing network. In line with this interpretation, the cerebellum and basal ganglia have been largely identified as key structures in sequencing and timing (Penhune et al., 1998; Nenadic et al., 2003; Ivry and Spencer, 2004; Tillmann et al, 2008; Callan et al., 2007; Schwartze et al.,

2012) and are also known to play a role in sensory-motor learning. The present coactivation of basal ganglia and cerebellum with frontal and parietal regions is coherent with previously reported structural connectivity between these regions (Bostan et al., 2013). Our results suggest a functional implication of this network in binding auditory information.

Although the activation of the right hippocampus found in the GLM was not significant on the parametric analysis at a robust threshold, a correlation was found between brain activity within the right hippocampus and memory performance across subjects in this condition. This correlation, which was not shown in the unified condition, supports our hypothesis for the greater implication of the hippocampus when encoding elements are presented separately. Correlations were also found for the right parahippocampal gyrus, the striatum (left caudate and right putamen) and right pallidum, suggesting the involvement of these structures in binding under the separate condition. This evidence suggests the cooperation of the right hippocampus with basal ganglia to bind lyrics and melodies that are presented separately. The striatum and hippocampus have previously been found to cooperate via the prefrontal cortex in a variety of tasks (Seger, 2006), including encoding of words (Sadeh et al., 2011; for a review see Battaglia et al., 2011), spatial navigation (Brown et al., 2012; Hartley and Burges, 2005), sequence learning and consolidation (Albouy et al., 2008; Kotz et al., 2009; Tubridy and Davachi, 2010; Schwartze et al., 2012; Albouy et al., 2013; Chan et al., 2013). This large body of research has challenged the competitive view on hippocampal and basal ganglia function, and led to a growing number of studies to also assess mnemonic functions of the striatum for both procedural and declarative memory (Scimeca and Badre, 2012; Badre et al., 2014; Censor et al., 2014). The present findings are in agreement with this new approach.

Another important finding highlights the combined activation of a cerebello-striatal circuit and the frontal activations shown by the parametric analysis. This is consistent with previous studies showing the implication of such a network on the integration of temporal structure and memory content, including processing of durations (Fuster, 1995; Hälbig et al., 2002) and subsequent long-term storage of temporal structure (Schwartze et al., 2012). Correlations between brain activity and memory performance for the separate condition were also found in the IFG bilaterally, in its orbital part in the left hemisphere, and in the opercular and triangular parts for the right hemisphere. This result contrast with binding in the unified condition, which engaged Broca’s are, highlighting the contribution of the right homologue (opercular and triangular parts of the right IFG) for the this condition. Laterality differences in the IFG have been previously reported in studies comparing singing to speech sounds (Merrill et al., 2012) with right and left lateralized activations respectively. Despite the fact that in our study songs were presented in both conditions, it is plausible that encoding under unified and separate conditions may have respectively rely more on the verbal (Opitz and Friederici, 2003) or on the musical structure (Koelsch and Friederici, 2003), resulting in the laterality differences in the IFG.

Interestingly, although previous studies describe a particular role of the posterior STG on song integration (Sammler et al., 2010; Alonso et al., 2014), our results did not show the involvement of this area in the separate condition. It is possible that integration effects found previously in this region may be dependent on the physical properties of songs that already integrate both components into an auditory signal, and thus are specific to encoding following the unified condition. Since lyrics and melodies were not initially integrated into an auditory signal during the separate condition, the profile of activity seen in response to this condition may correspond to a more independent perceptual processing of lyrics and melodies. In turn, the binding of song elements under the separate condition may have enhanced the involvement of other structures such as the right hippocampus, left caudate and cerebellum to bridge the gap between lyrics and melodies and finally encode the integrated song representation.

It is worth mentioning that the MTG and other reported SME modulation of activity in areas such as the IPL, the SFG or the anterior cingulum, have also been reported to contribute to the inhibition of overt responses in language, essential for covert production of inner speech (Perrone-Bertolotti et al., 2014), similarly to the demanded auditory imagery of songs. From another perspective, a role for the MTG has also been reported for singing (Brown et al., 2004) and music memory retrieval (Watanabe et al., 2008). Although we interpret the present findings in this context, it should be noted that the MTG also holds a relevant function for processing complex linguistic lexical-meaning relations required for reading. Thus, alternatively, reading might have enhanced the activation of the left MTG, found both during unified and separate conditions. Nevertheless, we did not expect a major involvement of a reading network since instructions for the task were to elicit an auditory mental representation of songs, and the recognition test did not provide any visual cue related to the song.

Finally, the parametric analysis also revealed SME in the left IPL. This multimodal associative region receives inputs from most of the structures that were shown in our results, including the caudate and the hippocampus (Seghier, 2013). The mental manipulation of lyrics and melodies for covert singing may have elicited the activation of the left IPL during encoding to support the integrated imagery of lyrics and melody. In contrast to the unified condition, the separate condition required higher mental manipulation of the stimuli for the integration of separately presented features, eventually boosting the involvement of the IPL. Activation of this region has been previously shown during multimodal processing, imagery tasks and mental manipulation of representations (Seghier, 2013). Particularly, activation in angular gyrus has been reported during mental imagery in music (Herholz et al., 2012) and perceptual binding of auditory information (Kamke et al., 2012). In line with this evidence, the inferior parietal sulcus has been recently implicated in the processing of temporal and pitch transformations with musical imagery (Foster et al., 2013), which may be particularly relevant for binding song components in the separate condition. This interpretation is in agreement with a study showing a role of areas surrounding the parieto-temporal boundary for audio-motor integration during mental imagery tasks such as covert rehearsal or humming of auditory stimuli (Hickok et al., 2003; Buchsbaum et al., 2005). In addition to the manipulation of mental representations (Foster and Zatorre, 2010; Foster et al., 2013), some studies have suggested a role of the IPL in working memory (Buchsbaum et al., 2005, 2011) as well as in episodic memory based in its co-activation with the MTL system during memory tasks (Shannon and Buckner, 2004; Wagner et al., 2005; Vincent et al., 2006; Vilberg and Rugg, 2008). Our results support this notion in the case of binding separate elements of songs. The fact that left IPL activation was also shown for the general task (for both conditions and irrespective of memory performance), suggest a general contribution of this region to mental imagery, which may have become crucial for binding processing in the separate condition.

Comparison between the two encoding conditions

The present study aimed at examining binding by looking at differences between the encoding of songs presented in a unified or in a separate condition. General task differences between the conditions, irrespective of memory performance showed that the unified condition elicited greater activation in the STG and MTG, together with the orbital part of the left IFG and the left anterior cingulum relative to the separate condition. The greater activation of the STG is in line with studies on song perception, which identify the posterior

STG as the substrate for integrated song representations (Sammler et al., 2010; Schön et al., 2010). Therefore, one possible explanation for these results is a greater perceptual richness for songs presented under the unified condition, since they already provide an integrated representation of the song. These data is also in agreement with our hypothesis of a greater involvement of the left IFG on the unified condition, given that this was the only condition in which melodic information was embedded in the verbal code. Moreover, no brain area showed greater activation for the separate as compared to the unified condition, further supporting the perceptual richness interpretation. However, as we have previously discussed the interpretation of these results is limited by the behavioral differences found between conditions.

Most importantly, we compared SME between the two conditions based on the parametric analysis. Results revealed greater SME modulation of activity in the separate as compared to the unified condition in various areas that seem to belong to an auditory-motor integration network (Zatorre et al., 2007; Brown et al., 2004), including the cerebellum, the left insula, left MTG, left anterior cingulate, right fusiform gyrus, right orbital IFG and, critically, the right hippocampus. These areas are relevant for the coupling of perception and action and have been already reported in studies involving speech and singing (Ackermann and Riecker, 2004; Callan et al., 2007, Herholz et al., 2012). In particular, the cerebellum seems to be crucial to provide a precise timing context (Janata and Grafton, 2003; Ivry and Spencer, 2004; Callan et al., 2007; Schwartze et al., 2012) in which lyrics and melodies could be bound when presented separately.

We suggest that the activation found on the left anterior cingulum is related to monitoring auditory feedback during covert singing (Zarate and Zatorre, 2008; Perry et al., 1998). This seems to be necessary to properly merge the pitch and rhythm with the corresponding frequency onset/offset and spectral patterns that contain the syllabic information, which is required for the separate condition and less for the mere repetition of songs in the unified condition. However, activity in the anterior cingulate cortex may also signal a difference in cognitive effort (Crittenden and Duncan, 2014) between the two kinds of binding. Although both conditions demanded participants to sing covertly in order to memorize the song, the separate condition required participants to be more actively engaged in binding lyrics and melodies, representing an unavoidable caveat in the present study. As attested by the broader number of regions implicated in this condition, and the behavioral difference in recognition between the two conditions, we cannot reject the possibility that differences in task difficulty may be in part responsible for the findings obtained by the contrast between conditions. In this context, anterior cingulum and fusiform gyrus, may in part reflect the more active engagement and cognitive effort of participants in the task under the separate condition. Although a difference in the cognitive demands between the two conditions presented here may be unavoidable, future studies should aim to minimize the difficulty level of the separate condition. Indeed the fact that few participants had to be excluded even after the pre-screening of participants suggest that the separate condition may have a high difficulty overall, so the results here presented are restricted to those who may be able to do the task successfully.

Consistent with our predictions, we found greater activation of the right hippocampus for the separate condition as compared to unified condition binding. This novel finding supports the involvement of the right hippocampus in binding lyrics and melodies, particularly when these elements are presented separately. The greater implication of the hippocampus on the separate condition is in line with similar studies in the visual domain suggesting an increasing involvement of the hippocampus with greater discontiguity of the elements to bind (Staresina and Davachi, 2009). However, a crucial novelty in our design is that subjects were asked to bind trial-unique information, as melodies from every song were different. Thus, the cognitive demands may differ from those in visual studies presenting a limited number of contexts (i.e. four colors) for possible binding (Staresina and Davachi, 2009). The results of this study are also in line with the implication of the right hippocampus and left IFG in music retrieval (Watanabe et al., 2008).

Although the present study represents a first step to address the implication of the hippocampus in binding songs, future studies isolating factors such as number of contexts, different salience, semantic content or rhythmical structure of the songs may help to improve the understanding of the binding function in the context of songs.

Conclusion

The present study examined the neural substrate underlying the binding of lyrics and melodies during encoding of songs. Overall, our results highlight the implication the right hippocampus along with an auditory-motor network engaged in timing and sequencing processing for binding song components following the separate presentation of lyrics and melodies. Conversely, binding in the unified condition highlights the role of the left IFG in binding verbal with melody information, providing evidence for its contribution in the specific case of song binding. Further studies using different types of auditory stimuli, as for instance voice identity or instrument timbre with melody, are encouraged to complete our understanding of binding auditory information within and between modalities. Here, we discuss and provide novel evidence for the role of the hippocampus in binding lyrics and melodies within songs. Furthermore, in light of these results, other structures such as the IFG, basal ganglia and the cerebellum may be additionally relevant for binding auditory information and their particular role should be explored in more detail by future studies.

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Table 1.a. Binding success scores according to accuracy and confidence

			Correct response	
			Correct “yes” (for original)	*Correct “no” (for rearranged)*
Subject response	*Yes*	*Sure*	0.5	-0.5
		Not sure	0.25	-0.25
	No	*Sure*	-0.5	0.5
		Not sure	-0.25	0.25

Table 1.b. Binding scores for fMRI analysis

	Memory scores	**GLM**
Both correct and sure	1	Hit
Both correct one sure	0.75	Hit
Both correct non sure	0.5	Hit
One correct sure & One incorrect not sure	0.25	-
One correct not sure & One incorrect not sure	0	Miss
One correct sure & One incorrect sure	0	Miss
One correct not sure & One incorrect sure	(-0.25) 0	Miss
Both incorrect non sure	(-0.5) 0	Miss
Both incorrect one sure	(-0.75) 0	Miss
Both incorrect and sure	(-1) 0	Miss

Table 2. Summary of behavioral results

	Separate condition			Unified condition			Demographic data				
Subject	**AUC**	**SD**	***p***	**AUC**	**SD**	***p***	**Plausibility**	**Age**	**Sex**	**Education**	**Musical expertise**
C01	0.589	0.055	0.110*	0.655	0.053	0.005	0.71	20	f	13	11
C02	0.658	0.053	0.005	0.822	0.042	0.000	0.79	21	m	15	7
C03	0.796	0.044	0.000	0.889	0.033	0.000	0.79	22	f	17	7
C04	0.503	0.056	0.963*	0.714	0.050	0.000	0.79	19	m	12	3
C05	0.547	0.056	0.395*	0.836	0.039	0.000	0.71	20	f	14	2
C06	0.551	0.056	0.363*	0.735	0.048	0.000	0.67	23	f	16	3
C07	0.837	0.040	0.000	0.785	0.044	0.000	0.67	23	f	18	4
C08	0.788	0.043	0.000	0.849	0.036	0.000	0.79	33	f	20	10
C09	0.733	0.049	0.000	0.811	0.042	0.000	0.67	21	m	16	3
C10	0.579	0.056	0.157*	0.664	0.052	0.003	0.75	31	f	17	6
C11	0.706	0.050	0.000	0.843	0.037	0.000	0.71	24	f	17	5
C12	0.639	0.053	0.013	0.685	0.050	0.001	0.71	25	m	17	4
C13	0.723	0.050	0.000	0.717	0.050	0.000	0.83	25	f	14	6
C14	0.718	0.049	0.000	0.867	0.037	0.000	0.67	25	m	16	4
C15	0.863	0.037	0.000	0.865	0.037	0.000	0.75	20	f	16	4
C16	0.687	0.051	0.001	0.701	0.051	0.000	0.71	21	m	16	10
C17	0.628	0.055	0.022	0.644	0.054	0.010	0.83	21	m	16	9
C18	0.763	0.046	0.000	0.800	0.042	0.000	0.79	21	m	16	2
C19	0.560	0.055	0.282*	0.645	0.053	0.009	0.75	43	m	17	4
C20	0.756	0.047	0.000	0.780	0.045	0.000	0.79	26	m	16	3
C21	0.504	0.056	0.941*	0.713	0.050	0.000	0.75	22	m	17	9
C22	0.683	0.051	0.001	0.801	0.044	0.000	0.75	24	f	16	4
MEAN	0.67	0.05		0.76	0.04		0.74	24.09	*11f*	16.00	5.45
SD	0.11	0.01		0.08	0.01		0.05	5.46	*11m*	1.69	2.79

* Performance at chance level. SD: standard deviation; *f*: female; *m*: male.

Table 3. GLM task effects

Cluster size (k)	MNI coordinates	Region	Side	Region size (k)	mean T
265	56, 0, 46	Precentral	R	216	4.152
		Middle frontal gyrus	R	49	3.997
9	48, 38, 28	Middle frontal gyrus	R	7	3.736
15	56, 32, 2	IFG triangular	R	15	3.652
6778	-66, -22, 8	IFG triangular	L	1664	4.589
		IFG orbital	L	440	4.658
		IFG Operculumcular	L	742	4.453
		Middle frontal gyrus	L	552	4.180
		Middle frontal gyrus Orbital	L	98	4.904
		Heschl gyrus	L	35	5.468
		Insula	L	213	3.875
		Postcentral	L	82	3.864
		Precentral	L	999	4.267
		Rolandic Operculum	L	97	4.280
		MTG	L	666	5.249
		Superior Temporal Pole	L	196	5.603
		STG	L	861	5.647
1623	64, -4, -2	STG	R	1008	5.494
		Superior Temporal Pole	R	297	4.829
		MTG	R	189	4.610
		Rolandic Operculum	R	34	4.225
		Heschl gyrus	R	26	5.049
		Middle temporal pole	R	9	3.970
1259	6, 2, 66	Supp Motor Area	L	569	4.299
		Superior Frontal gyrus	L	245	4.021
		Supp Motor Area	R	205	4.496
		Middle frontal gyrus	L	140	3.867
		Superior Frontal gyrus (medial)	L	95	3.789
667	-48, -44, 52	Inferior Parietal lobe	L	382	3.862
		SupraMarginal	L	161	4.017
		STG	L	96	3.910
13	-20, -72, 6	Calcarine	L	13	3.489
2295	28, -64, 6	Calcarine	R	704	4.009
		Cerebelum VI	R	573	4.332
		Calcarine	L	312	3.839
		Cerebelum Crus1	R	308	3.973
		Lingual	R	175	4.010

		Cuneus	R	56	3.825
		Cuneus	L	44	3.932
		Superior Occipital gyrus	R	35	3.872
		Vermis VI		33	3.979
		Middle Occipital gyrus	R	19	3.778
		Fusiform	R	15	3.799
63	-8, -74, -14	Cerebelum VI	L	57	3.700
		Lingual	L	5	3.560
195	-42, -66, -26	Cerebelum VI	L	110	3.848
		Cerebelum Crus1	L	85	4.001
250	-22, -70, -58	Cerebelum VIII	L	149	4.628
		Cerebelum VIIb	L	8	4.075
918	30, -64, -52	Cerebelum VIII	R	536	4.731
		Cerebelum Crus2	R	228	3.762
		Cerebelum VIIb	R	128	3.836
		Cerebelum Crus1	R	14	3.659
17	-20, 2, 8	Putamen	L	16	3.646
10	20, -6, 24	Caudate	R	10	3.529

Table 4. GLM analysis of encoding

Unified: successful > unsuccessful					Separate: successful > unsuccessful				
Region	**Side**	**Size (k)**	**MNI coordinates**	**t**	**Region**	**Side**	**Size (k)**	**MNI coordinates**	**t**
IFG- triangular	L	18	-46 34 4	4.346	MFG	L	7	-28 32 30	4.078
Postcentral gyrus	L	20	-64 -18 20	4.110	MTG	L	6	-48 -4 -16	3.91
MTG	L	9	-66 -28 2	4.113	Cerebelum IX	L	11	-2 -52 -44	4.055
MTG	R	6	46 -22 -12	4.210	Caudate	L	10	-6 14 -2	4.029
					Vermis III	V	2		4.032
					SFG	R	8	22 40 34	4.421
					IFG- orbital	R	5	44 24 -10	4.211
					Cerebelum III	R	3	6 -42 -10	3.881
					Hippocampus	R	6	30 -18 -12	3.974

Table 5. Parametric analysis of encoding

Unified

Region (aal)	Cluster size (k)	Region size (k)	x,y,z {mm}	Z
Left hemisphere				
Middle temporal gyrus	7	7	-48 -16 -12	3.42
IFG- triangular	9	8	-44 34 -2	3.39
Postcentral gyrus	5	4	-52 -4 16	3.30
Right hemisphere				
no significant activations				

Separate

Region (aal)	Cluster size (k)	Region size (k)	x,y,z {mm}	Z
Left hemisphere				
MTG	23	23	-60 -8 -22	3.78
SFG (medial)	8	6	-12 26 60	3.77
SFG (medial)	24	23	-2 52 16	3.36
IPL	6	5	-62 -48 36	3.57
Caudate	29	27	-6 12 -2	3.89
Anterior cingulum	30	25	-4 38 4	3.56
Cerebellum IV - V	8	4	-14 -32 -16	3.49
Right hemisphere				
SFG (medial)	10	8	2 62 14	3.33
MFG (p. orbitalis left)	43	30	0 42 -10	3.53
Fusiform gyrus	5	1	34 -70 -8	3.40
Caudate	6	6	10 10 -10	3.18
Vermis III	24	9	8 -46 -12	3.82
Cerebelum II	71	54	24 -84 -38	4.20
Cerebellum X	5	3	18 -38 -42	3.74

Unified > Separate

Region (aal)	Cluster size (k)	Region size (k)	x,y,z {mm}	Z
no significant activations for this condition				

Separate > Unified

Region (aal)	Cluster size (k)	Region size (k)	x,y,z {mm}	Z
Left hemisphere				
MTG	30	30	-56 -4 -22	4.27
Insula	16	11	-38 -12 -4	4.58

Anterior cingulum	9	9	-6 40 6	3.45
Anterior cingulum	7	5	-4 30 14	3.60
Cerebellum IV - V	45	20	-14 -30 -14	3.73
Vermis IV -V	18	7	-4 -64 -10	3.49
Right hemisphere				
IFG (p. orbitalis)	8	6	32 18 -22	3.33
Fusiform gyrus	43	32	24 -74 -14	3.79
Fusiform gyrus	6	5	26 -56 -12	3.27
Right hippocampus	6	6	32 -20 -12	3.36
Vermis III	43	23	6 -42 -10	3.85

Significant clusters ($p < 0.001$; $k \geq 5$), and the regions within them from the "automated anatomical atlas".

Table 6. Parametric binding within ROIs correlated with AUC $p < 0.05$

Unified: successful > unsuccessful			Separate: successful > unsuccessful		
Region of Interest	**Pearson correlations**	***p* *(1-tailed)***	**Region of Interest**	**Pearson correlations**	***p* *(1-tailed)***
Left hemisphere			***Left hemisphere***		
IFG (opercularis)	0.391	0.036	IFG (orbitalis)	0.381	0.040
IFG (triangularis)	0.392	0.036	Caudate	0.408	0.030
Right hemisphere			***Right hemisphere***		
			IFG (opercularis)	0.443	0.019
			IFG (triangularis)	0.366	0.047
			Hippocampus	0.442	0.020
			Parahippocampal gyrus	0.384	0.039
			Pallidum	0.466	0.014
			Putamen	0.519	0.007

Figure 1. Experimental trials

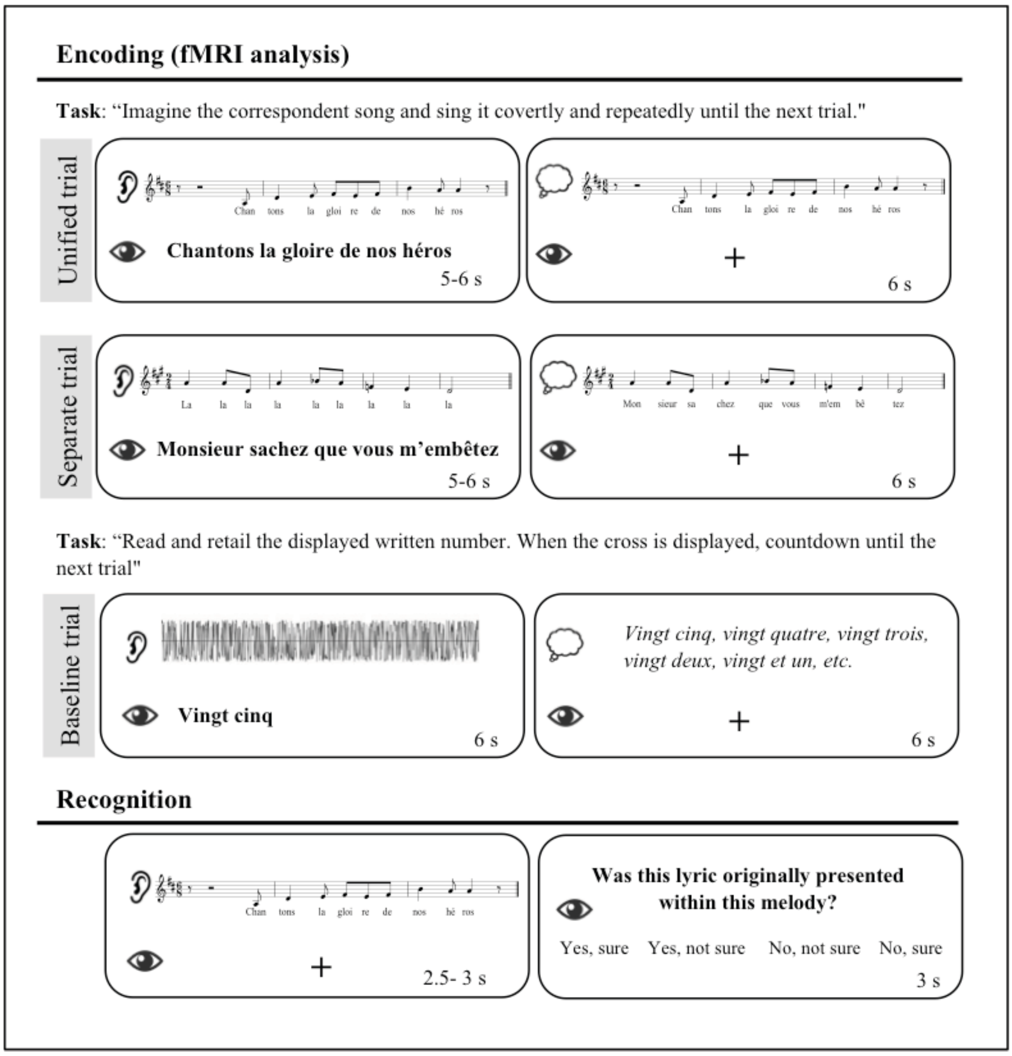


Figure 2. Scanning session

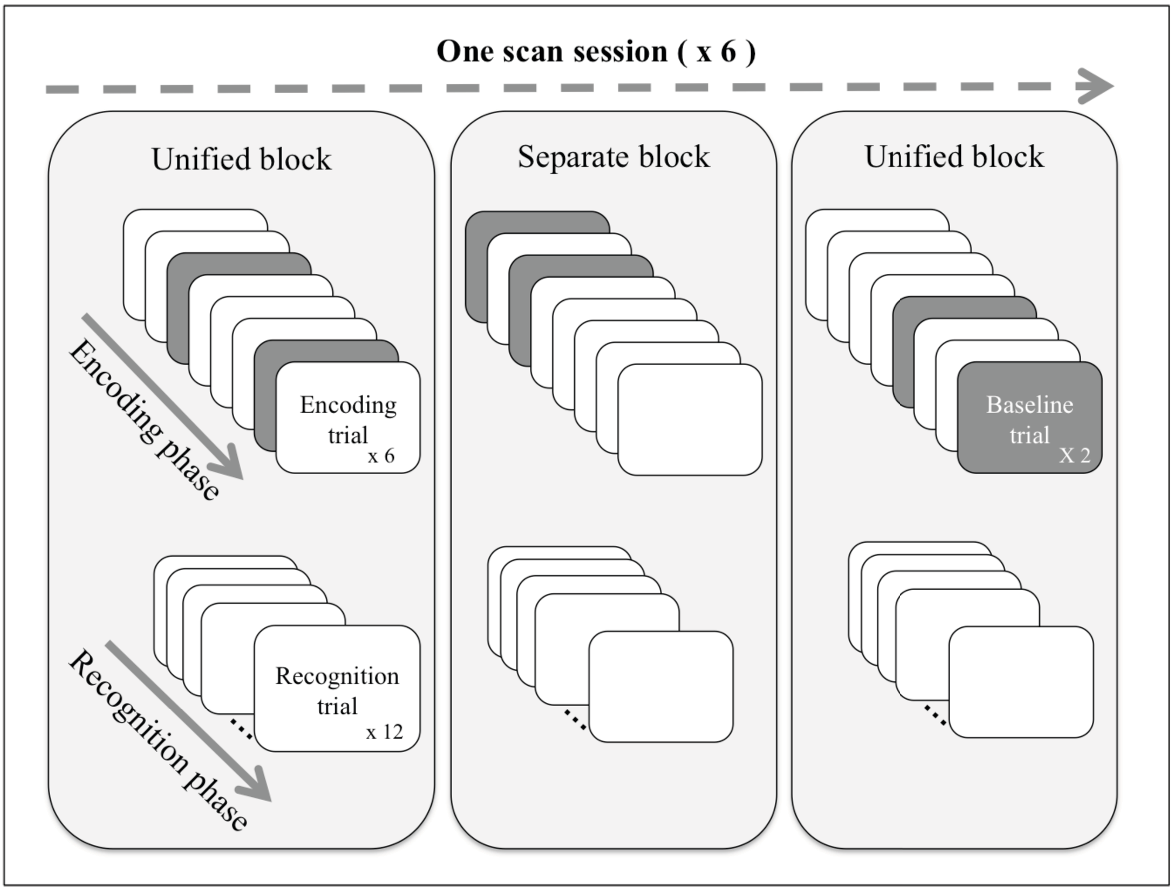


Figure 3. General task effects.

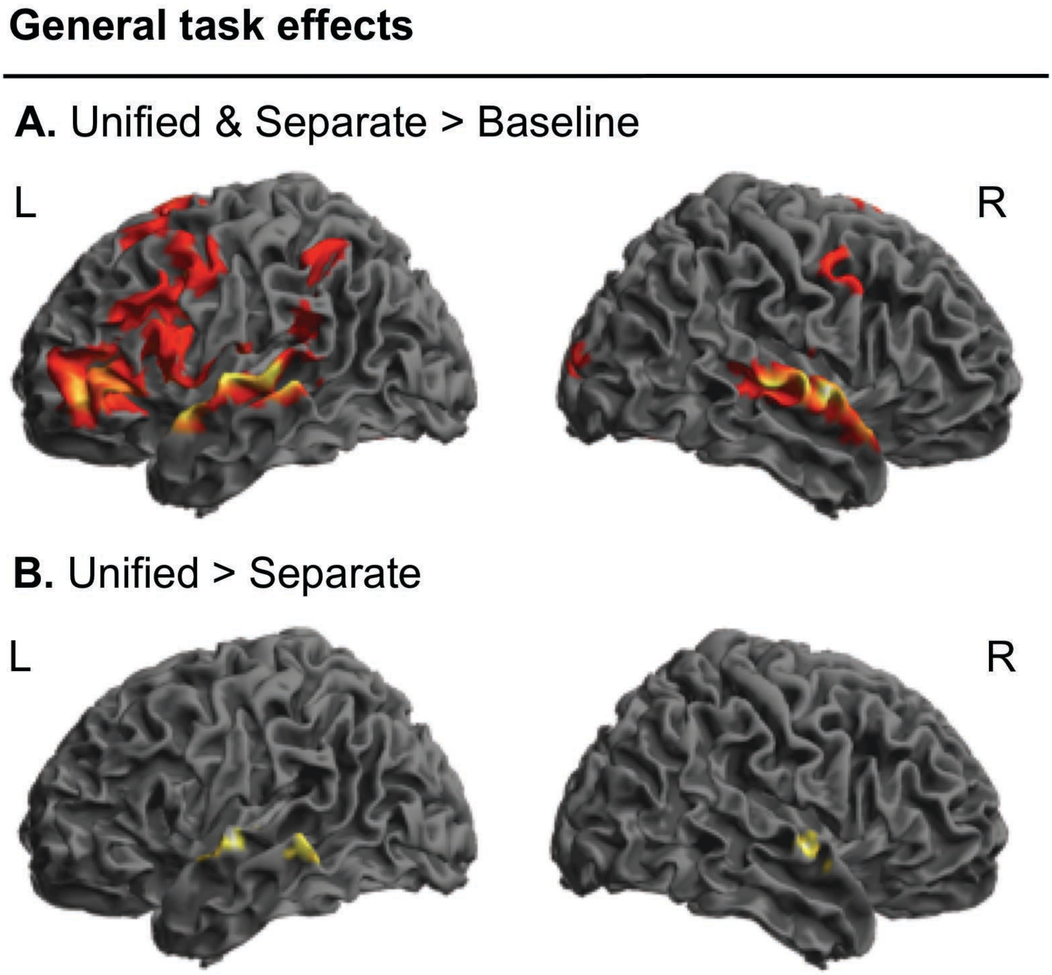


Figure 4. GLM subsequent memory effects

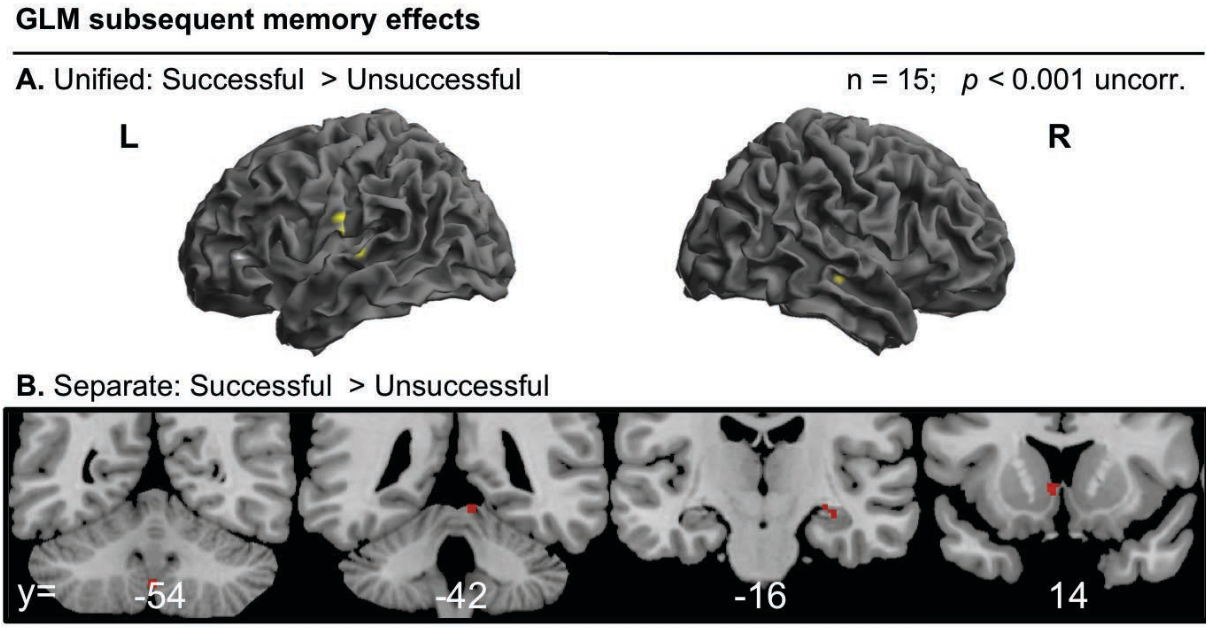


Figure 5. Parametric analysis subsequent memory effects

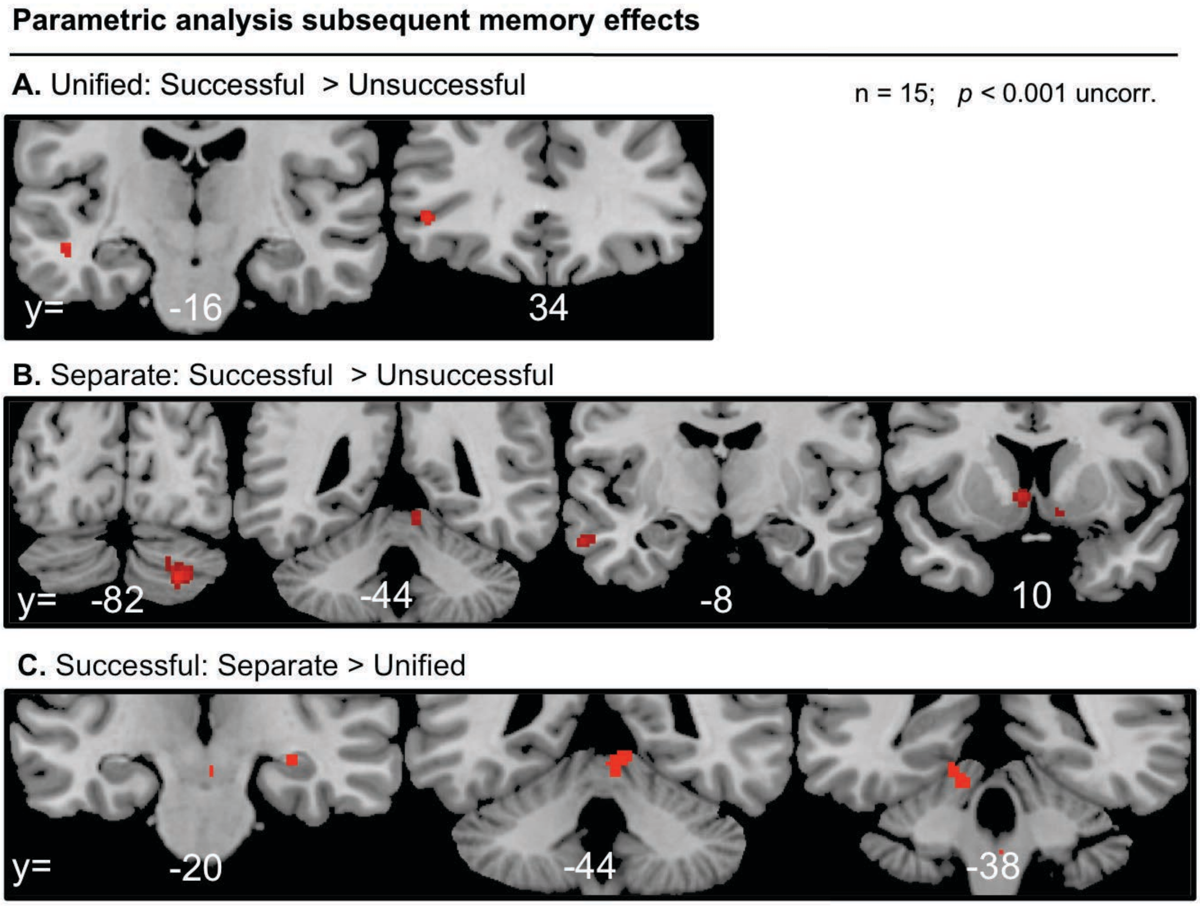
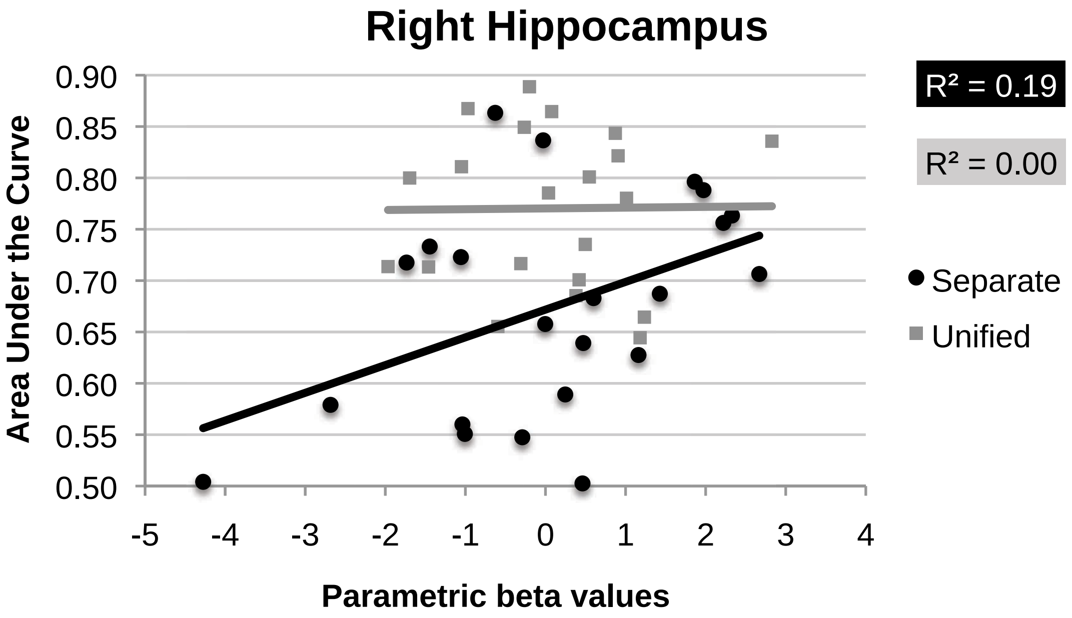


Figure 6. Correlation between BOLD activation and memory performance in the right hippocampus



Chapter 7 : Binding lyrics and melodic context in memory for songs following unilateral temporal lobe excision including the hippocampus.

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Abstract

Memory for songs requires binding of lyrics and melodies - a function that may be mediated by the medial temporal lobe. We conducted a neuropsychological study with patients presenting an unilateral temporal lobe excision to investigate the role of the medial temporal lobe on binding lyrics with their melodic context. In line with our hypothesis, a strong deficit in lyrics recognition was shown in LTL as compared to Controls. Although RTL performed better than LTL in lyrics recognition, a weak deficit was shown when compared to Controls. The correlation found between verbal memory measures and lyrics recognition suggest that when lyrics are merged in melodies, the slight verbal deficits present in some RTL patients may be amplified. We provide evidence for dissociation between explicit recognition of the melody context and its implicit influence on lyrics recognition, suggesting that medial temporal lobe structures may be crucial for encoding the detail binding of lyrics with their melodic context, whereas implicit effects of an integrated representation of the song may be spared after medial temporal lobe lesions. These results suggest that although memory for lyrics may involve more strongly the left temporal lobe, binding of lyrics with their melodic context recruits regions of both temporal lobes. The implication of these findings is discussed in relation to the neuroimaging literature.

Keywords: songs, music, verbal, memory, binding, hippocampus, temporal lobe lesion.

Introduction

To form a memory of a song, lyrics need to be bound to their melodic context into a unified memory trace. In the visual domain, the binding of different elements into a unified memory trace has been shown to be dependent on the hippocampus and surrounding cortex of the medial temporal lobes (MTL) (Davachi, 2006; Diana et al., 2007; Ranganath, 2010). However, the role of the MTL in binding lyrics and melodies in songs remains poorly understood. A neuropsychological approach assessing memory for songs in patients with MTL lesions could shed light on this issue. The aim of the present study is to examine the differential implication of left and right MTL structures on the binding of lyrics and melodies in the memory for songs.

To understand the processing involved in song encoding, it is important to first take into account the perceptual integration of lyrics and melodies. Indeed, a growing body of evidence suggests that memory emerges from perception (Graham, 2006; Lee et al., 2005; Lee and Rudebeck, 2010a, 2010b; for a review see Bussey and Saksida, 2005; Graham, 2010). Perception will preclude encoding through a dynamic network between the hippocampus and the cortex that constantly updates the existing information with new encountered events (for a review see Sashtri, 2002). Few neuroimaging studies in song perception have described the neural substrate for the integration of lyrics and melodies (Schön et al., 2010; Sammler et al., 2010). These studies agree on the involvement of the posterior areas of the superior temporal gyrus (STG) and superior temporal sulcus (STS) for the integration of lyrics and melodies. In addition, Sammler and colleagues (2010) found independent activity specific for the lyrics as compared to the melody in the left anterior STG and the left temporal pole. The presence of such lyric independent component in the absence of a melody analog effect, suggest that the weight of these components in song processing may not be equally distributed.

In a recent study (Alonso et al., 2014a), we applied the fMR-adaptation paradigm adapted for songs by Sammler and colleagues to assess the effects of unilateral hippocampus sclerosis in such perceptual integration of songs. This paradigm allows an identification of areas involved in lyrics and/or melody processing based on the expected reduction of neural activation following the differential repetition of each song feature. Reduction of activation as a result of stimuli repetition (adaptation) revealed areas of song processing along the STG and STS bilaterally in healthy participants as previously reported (Sammler et al., 2010). However, significant lack of adaptation was found in left hippocampal sclerosis patients both for lyrics and for the integrated processing of songs, indicating a role for the left hippocampus in song integration. Although right hippocampal sclerosis patients showed smaller areas of adaptation as compared to healthy participants, differences between these groups on the adaptation effect were not significant. Overall, despite the lack of direct evidence for hippocampal activation during perceptual integration, these neuropsychological results suggest that left hippocampus in particular may exert a feed forward influence in the creation of an integrated representation that could precede the emergence of a bounded memory trace. Therefore, when lyrics and melodies are presented as a unified song, left temporal structures seem to be more important than right temporal areas for song integration.

From a more strict memory perspective, several behavioral studies have measured memory for melodies and lyrics (Crowder et al., 1990; Peretz et al., 2004; Peynircioglu et al., 2008; Serafine et al., 1984, 1986). One very straightforward approach to this issue has been the examination of a memory of familiar songs by looking at cuing effects of the lyrics on melodies and vice versa (Peretz et al., 2004; Peynircioglu et al., 2008). Peretz and colleagues (2004) conducted a series of priming studies manipulating the presentation of lyrics and melodies from familiar songs as primes, as well as targets and assessing the cuing effects within (melody-melody; spoken text- spoken text) and between modality (melody-spoken text; spoken text-melody for each song element). Their results measured by accuracy and reaction times suggest a robust reciprocal ability for one song element to prime the other, suggesting a tight association between lyrics and melodies in song memory traces in healthy participants. However, in a later experiment, Peynircioglu and colleagues (2008) showed that lyrics are better cues to melodies than vice versa, and better recognition of lyrics than melodies, highlighting the strength of lyrics for song recognition. Nevertheless, since this studies evaluated semantic memory for familiar songs, the processing of lyrics and melodies may be different than that required for the encoding of a novel song.

Using a different approach, Serafine, Crowder and Repp (Crowder et al., 1990; Serafine, 1984, 1986) examined episodic memory for new learned songs in healthy participants. Participants had to recognize lyrics and melodies of previously studied songs.

Lyrics and melodies of the *original* songs were manipulated to create song lures, including songs with old lyrics and new melodies, new lyrics with old melodies, fully new songs, and songs that had old lyrics and old melody but *rearranged* in a wrong combination. A song integration effect was found whereby lyrics and melodies were better recognized when presented within the original songs in which they were studied than when they were presented in a rearranged song, and it could not be eliminated by voluntary attention to the melody (Serafine et al., 1984). This result persisted when semantic factors were eliminated by using non-words and a possible decrement in recognition due to distracting effects of the novel lyric, or the melodic context was ruled out by further experimental manipulations (Serafine et al., 1996).

A later study (Crowder et al.,1990) was designed to contrast two possible explanations for this effect. One explanation was based on a qualitative interaction of the physical characteristics of the particular lyrics and the melody, in other words, resulting in a bonded percept (Exp. 2). The second explanation was based on a contiguity hypothesis suggesting that associations may be boosted just by the mere temporal co-occurrence of lyrics and melodies (Exp.3). Although a contiguity effect was shown, evidence supporting a bonded percept was found in the Experiment 2, showing better memory for melodies when presented with non-words phonologically similar to the original non-words with which they were studied, than when presented with phonologically different non-words. Thus, these results argue in favor of a memory benefit in song recognition following the combined encoding of songs in healthy participants.

Conversely, patients with temporal lobe resections have shown clear deficits in the combined encoding of lyrics and melodies (Samson & Zatorre, 1991). Using the song memory recognition paradigm from Serafine and colleagues (1984), the recognition of lyrics, melodies and songs was assessed in patients who had undergone the removal of unilateral anterior temporal lobe for the relief of epilepsy. Memory for unfamiliar song elements was tested either after the presentation of songs (Exp 1) or in two independent tests which presented only the melody and only the spoken test respectively (Exp 2). These authors hypothesized a dual encoding of songs based on verbal and musical codes that would depend on the left and right hemisphere respectively. These patients performed two recognition memory tasks for melodies and lyrics and their performance was compared to the healthy controls. Results showed that all subjects recognized the lyrics better than the melodies, in agreement with more recent studies on healthy participants highlighting the predominance and greater autonomy of lyrics over melodies in song processing (Sammler et al., 2010). Recognition of lyrics was impaired only after the left temporal lobe damage. Conversely, recognition of melodies was impaired after both right and left temporal lobe lesions, when presented with new words, whereas only the left temporal lobe lesioned patients showed a melody recognition deficit if when melodies were presented with old words. Taken these results, it is possible that memory for melodies may have been mediated by verbal processing, so that patients with right temporal lobe lesions could succeed in this task when melodies were presented with old words. Conversely, for patients with a left temporal lobe lesion the presence of lyrics, either old or new, seem to disrupt melodic recognition.

The results from Exp. 2 clarify the interpretation of Exp.1. When memory for spoken text and melodies was tested independently, a dissociation was shown with deficits on spoken text recognition following left but not right TL damage and deficits for melodic recognition following right but not left TL damage. Thus, melody recognition impairments of left TL damaged patients previously shown in Exp. 1 seem to arise by the failure to integrate the verbal information into the melody, suggesting a binding role for left temporal structures. These results suggest that the integration of lyrics and melody would be affected in both patient groups.

Interestingly, although some of these findings speak for the independence of lyrics and melodies, a complete independence between the two would have had involved similar patterns of results when lyrics and melodies were presented separately (Exp 2.) or when they were presented unified into a song (Exp 1.), which was not the case. Indeed, the results obtained in this lesion study suggest that lyrics and melodies presented together in a song may be less accessible than when they are presented separately. Since memory for each element was tested independently in two different conditions, this indicates that the verbal and the melodic memory codes may need an additional integration processing to create a unique representation of the song, which is in line with the literature previously discussed. Integrated processing was also supported by better recognition of melodies when they were presented with the original lyrics than when they were presented with lyrics from other previously studied song. This suggests that melody recognition may be enhanced by its integration with lyrics into a song. Interestingly, words were similarly recognized in both conditions, reflecting a more independent and robust process for lyrics recognition. Nevertheless, only four original and four mismatched songs were used for recognition so this effect must be interpreted carefully.

Unfortunately, the TL damage of the patients in Samson and Zatorre (1991) was very extended and very variable between patients. Anterior structures to Heschl's gyrus as amygdala or temporal pole were always removed but hippocampus, parahippocampal gyrus and also Heschl's gyrus, which might have been very relevant for melodic processing (Patterson et al., 2002), were resected in different amounts. Thus, the amounts of MTL damage or the differential removal or spear of the hippocampus, which can be a crucial factor to interpret the memory outcome, were not under strict control.

In a recent neuroimaging study (Alonso et al., 2014b), we have assessed binding of lyrics and melodies during song encoding in healthy participants. Songs were presented under two different encoding conditions. In the unified condition melodies sung with lyrics were presented whereas on the separate condition melodies sung on the syllable “la” and written lyrics were simultaneously presented and participants had to reconstruct the song corresponding to the combination of the written lyrics with the melody. The results found a greater implication of the right hippocampus on binding in the separate condition as compared to the unified condition. Conversely, the unified condition seemed to rely more on the left IFG and STG regions. This suggests that sung lyrics, which integrate both melody and lyrics, provide a richer perpetual integrated representation of the song, consequently recruiting STG regions and eventually been driven by similar mechanisms in the left IFG that bind verbal information (Opitz et al., 2010). However, the lack of hippocampal responses in relation to subsequent memory following a unified song presentation in this study do not eliminate the possibility that the left hippocampus may still exert a feedforward function in a similar manner as for perceptual integration (Alonso et al., 2014a). Indeed, looking at activations of the successfully encoded trials on the unified condition revealed a left hippocampal cluster, which might have failed to rich significance in the later contrast.

The present study has been designed to better understand the effect of unilateral medial temporal lobe lesions on binding lyrics and melodies for the encoding of new songs. Patients with unilateral temporal lobe excision including the hippocampus as well as healthy controls were tested on a song recognition memory task including lyrics and melodic context recognition. The aim of this study was to assess both recognition of binding between lyrics and their melodic context a swell as lyrics recognition alone (irrespective of melodies). Based on the literature on similar patient populations (Samson and Zatorre, 1991) and similar musical tasks here described (Alonso et al., 2014b), we predicted that a left temporal lobe lesion (LTL) to impair both lyrics recognition alone and binding of lyrics with melodies recognition. On the other hand, we predicted that the right temporal lobe lesion (RTL) would spare lyrics recognition but impair the recognition of binding lyrics and melodies as compared to the healthy controls.

Methods

Participants

Twenty patients with unilateral resection of the anterior temporal lobe including the hippocampus (n=10 left hemisphere) participated in this study. Patients had undergone anterior temporal lobectomy for the relief of intractable temporal lobe epilepsy at the Pitié-Salpêtrière Hospital in Paris. The minimum post-surgical delay was one year (mean post-surgical delay LTL= 4.10 ± 1.73; RTL= 5.70 ± 3.83). Epileptogenic lesions were always static and of an atrophic nature. The surgery included the removal of the amygdala and the hippocampus, and to a variable extent, the perirhinal, the parahippocampal cortex, and the temporal pole. A representative lesion is shown in Fig. 1. Visual inspection of the post-operative MRIs by a neurologist categorized the lesions as selective amygdalohippocampectomy (SAH) (Dupont et al., 2001) (LTL: 7 patients; RTL: 4 patients), or anterior temporal lobectomy (ATL) (LTL: 3 patients; RTL 5 patients). The MRI from one RLT patient was missing. All patients included in this study were right handed as attested by the Edinburgh Handedness Inventory (Oldfield, 1971) except for one left TL patient that was ambidextrous and a right TL patient that was left handed. However, language lateralization to the left hemisphere in these patients was confirmed by preoperative independent MRI and both of cases had neuropsychological profiles and responses in the experimental test that were similar to their respective groups. In both cases the neuroimaging result confirmed that language was lateralized to the left hemisphere.

Additionally, a group of 19 healthy control French right-handed volunteers were recruited and selected to match the patients groups in terms of sex, age (F= 1.32; df: 2; 36; $p >$ 0.05), and years of education (F= 2.30; df: 2; 36; $p > 0.05$).

Music experience was balanced across groups as attested by the Ehrlé Music expertise questionnaire (Ehrlé, 1998) and no professional musician was included in this study. All participants had normal auditory imagery capabilities as measured by the French version of the Bucknell Auditory Imagery Scale (BAIS) (Zatorre et al., 2010). Demographic characteristics of the groups are summarized in **Table 1**.

Neuropsychological data from both patient groups is shown in **Table 2**. All patients from this sample had normal IQ scores as measured by the full scale WAIS-R. Direct digit span scores indicated that verbal short-term memory was not impaired in these patients. However, a verbal memory deficit, as assessed with the Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964; Sziklas & Jones-Gotman, 2008) (Total recall score consisting in the addition of the five successive recall, *∑R1-R5 RAVLT*), was present in the LTL group. A univariate ANOVA on RAVLT total recall scores revealed significant group differences (F= 8.98; df: 2, 36; $p < 0.01$; $h^2 = 0.33$). Multiple comparisons with Bonferroni correction showed that a deficit was present in LTL as compared to the normal healthy independent group ($p <$ 0.01) whereas this deficit was not observed for the RTL patients ($p > 0.05$). Furthermore, the LTL group performed significantly in the RAVLT than the RTL group ($p < 0.05$). This neurological profile highlights the functional differences between the two patient groups.

The local ethics committee approved this study in accordance with the Declaration of Helsinki and informed consent was obtained from each participant.

Stimuli

The stimuli consisted of 72 unfamiliar songs created based on a collection of 19th Century French folk songs (Robine 1974). Each lyric consisted of 6 to 9 pronounced syllables and each melody consisted of 6 to 9 notes. Syllables were matched to musical notes in a one-to-one basis. The songs had a variable duration between 2.5 to 3 seconds.

We combined 12 pairs of melodies with 12 pairs of lyrics and an additional list of 12 lyrics (new-lyrics) to form our stimuli set. Lyrics and melodies within pairs were interchangeable, allowing each of the melodies within a pair to be combined with three lyrics (the two from the lyric pair, and a third lyric) (see **Table 3**).

A first set of 24 songs was created by combining the 12 pairs of melodies with the 12 pairs of lyrics, conforming the *original* songs, which were used during the encoding phase. Another set of 24 songs (*rearranged* songs) was created by rearranging the lyrics and melodies of *original* song pairs. By following this procedure, the level of familiarity for lyrics and melodies remained equivalent for the *original* and *rearranged* songs. Additionally, 12 new-lyrics were combined with the 12 melody pairs, such that each new-lyric was combined with both melodies of the pair, creating 24 *new-lyrics* songs. In this way, each lyric was always combined with both melodies of the pair.

Procedure

The task consisted of 6 blocks including a study phase and a recognition phase each, and was presented in 1 of 4 pseudo-randomized orders. During the study phase participants studied 4 *original* songs. Songs were repeated twice in a row to facilitate perception and encoding. After listening to each song, a period of six seconds with a fixation cross was presented and participants were instructed to covertly rehearse the song during this time and try to memorize it for a subsequent recognition memory test. During the recognition phase 4 *original,* 4 *rearranged* and 4 *new-lyrics* songs were presented in random order. After listening to each song, participants were prompted with three yes/no questions. First they were asked to recognize the lyrics of the song (*Have you already heard this lyrics?).* If the answer was positive (*yes*, regardless of the accuracy of the response), participants were prompted with another question about the melodic context (Were this lyrics previously sung on this melody?). Finally, participants provided a confidence rating of their response (*Are you sure of your response?).* Each participant was tested individually and had the chance to learn the rules of the test in an example trial prior to the start of the experiment, where study and recognition phases and the three kinds of songs were illustrated and explained. Thus, participants were well aware that no new melodies would be presented during the recognition phase and that they had to recognize the lyrics followed by the combination of the lyric with the melodic context. Altogether, a total of 24 *original* songs had to be recognized among 72 songs, with an overall duration of the experiment of approximately 30 minutes.

Data analysis

Behavioral data from the recognition phases were analyzed in PASW statistics v18.0. Memory for the lyrics (item recognition), and for the binding of lyrics with their melodic context (binding of item with context) was addressed separately. Lyrics recognition performance was computed using the sensitivity index *d'*, which is a non-biased measure of recognition based on the hits and false alarms. Accuracy on responses to the first question for old-lyric songs (*original* and *rearranged* songs) and for *new-lyrics* songs as foils was taken into account.

For the melodic context recognition, Receiving Operating Curves (ROC) were drawn and the area under the curve (AUC) was calculated taking into account both accuracy (second question) and confidence (third question).

We used a One-way ANOVA on each dependent measure (*d'* for lyrics recognition and AUC for melodic context recognition) to test for group differences. Sex, years of education and age were included in the analysis as covariates. Additionally, *d'* scores for lyrics recognition in original song context, and in rearranged song context were computed. Then, original and rearranged song *d'* scores were compared using a repeated measures ANOVA with melodic context as a within subject factor and group as the between subjects factor.

Results

Lyrics recognition

All participants successfully recognized lyrics above chance (see Table 4). Data was normally distributed (Kolmogorov-Smirnoff D= 0.12; df= 39; $p > 0.05$), and variances were homogeneous between groups (Levene = 1.63, df= 2; 36, $p > 0.05$). The ANOVA on *d'* scores for lyrics recognition revealed significant group difference (F= 34.46; df= 2; 33; $p < 0.001$; $h^2 = 0.68$). Post-hoc pairwise comparisons, with Bonferroni correction for multiple comparisons, showed significant differences between Controls and LTL ($p < 0.01$); Controls and RTL ($p < 0.05$); and RTL and LTL ($p < 0.01$). These results indicate that lyrics were better recognized by Controls than both patients groups, and better recognized by RTL as compared to LTL (see **Fig. 2**). Age significantly covaried with *d'* (F= 7.16; df= 1;33; $p < 0.05$), indicating that performance on lyric recognition decreases with age. However, sex ad years of education did not show covariance with *d'* scores. To further explore this effect, a correlation between verbal memory measured by the RAVLT and results in lyrics recognition was calculated, showing a significant positive correlation between these factors (r= 0.53; $p < 0.05$) (see **Fig. 3**).

Melodic context recognition

Although most healthy participants succeed in recognizing melodic context (84.22% of participants above chance), this was not the case for patients since only 20% LTL and 30 % of RTL patients recognized song binding above chance level (see **Table 4**). Data was normally distributed (Kolmogorov-Smirnoff D= 0.07; df= 39; $p > 0.05$), and variances were homogeneous between groups (Levene = 1.172, df= 2; 36, $p > 0.05$). Results of the ANOVA for melodic context recognition revealed significant group differences (F= 8.09; df=2; 33; $p = 0.001$; $h^2 = 0.33$). Post-Hoc Bonferroni correction was applied to pairwise comparisons, showing significant differences between Controls and LTL ($p < 0.01$) and between Controls and RTL ($p < 0.05$). RTL and LTL were not statically different ($p > 0.05$). These results indicate that both patient groups were equally impaired for binding recognition as compared to Controls (see **Fig. 4**). Sex, years of education and age did not show covariance with AUC scores.

The effect of melodic context on lyrics recognition

The effect of melodic context on lyrics recognition was tested using a repeated measures ANOVA. The data analysis showed the main effect of melodic context on lyrics recognition (F= 11.32 ; df= 1,36 ; $p < 0.01$; $h^2 = 0.21$) (see **Fig. 5**). No interaction was found between melodic context and group.

Discussion

In the present study we assessed the effects of unilateral anterior temporal lobe resection, including the hippocampus, on memory for songs. During the recognition, lyrics and melodies of original songs were manipulated, presenting the lyrics (old or new) and their melodic context (original or rearranged) in song lures to measure memory for lyrics and for binding between lyrics and the melody. Binding effects were measured both by looking directly at the recognition of the correct melodic context, but also assessing the influence of melodic context on the lyrics recognition.

Lyrics recognition

As hypothesized, the LTL group was strongly impaired on lyrics recognition as compared to RTL and controls, supporting the left lateralization of lyrics encoding. Surprisingly, the RTL group also showed worse recognition of lyrics than controls. Nevertheless, it is worth noting RTL lyric recognition performance was significantly better than that of LTL patients. These differences cannot be attributed to differences in intelligence since both patient groups had normal IQs and the level of education was similar among the three groups. However, although RTL did not show a significant verbal impairment as shown by the RAVLT, their scores were slightly lower than that of the controls. It is possible that embedding verbal information into the melodies may have magnified the differences in verbal memory between controls and patients. Of note, it has been suggested that the recognition of lyrics in a song may be harder than on the presentation of spoken lyrics (Samson and Zatorre, 1991), which may account for the present RTL deficit. In addition, few case studies (Peters et al., 2009) have supported the influence of right medial temporal lobe regions on verbal recollection, in agreement with the present results. Indeed, the global correlation found between lyrics recognition and verbal memory further supports this interpretation. Thus, we suggest that the present deficit in RTL is more likely to be related to verbal memory deficits.

Based on the prosody literature, another alternative interpretation involves deficits in contour aspects of verbal processing that are known to be right lateralized (Buchanan et al., 2000; Dara, 2014; Gordon et al., 2011; Pell, 2006; Ross, 1988; Zatorre & Baum, 2012; for a review see Frederici, 2011; Lindell, 2006). Although the spared left hemisphere carries the major processing of verbal information, prosodic components may be intrinsically paired with lyrics encoding, accounting for the deficit found in RTL patients. However, this interpretation is at odds with findings by Adolph and colleagues (2001), who have shown that emotional prosody recognition was spared after anteromedial temporal lobe excision. It is nevertheless possible that such finding remain specific to emotional information. Interestingly, a neuroimaging study comparing the processing of pitch patterns in song and speech revealed that prosody in speech involved left lateralized activations in contrast with the pitch processing in a song that was right lateralized (Merril et al., 2012). Taking these findings into account, it is possible that the RTL deficit in lyrics processing may be related to the melodic processing in the lyrics, beyond a prosodic deficit. In other words, if binding of lyrics and melodies may account for lyrics recognition, a deficit in binding could affect the recognition of the elements, in this case the lyrics.

Binding of lyrics and melodies

To test the binding of lyrics and their melodic context in memory, we looked at explicit melodic context recognition within recognized lyrics trials, as well as the implicit effect of melodic context in lyrics recognition.

In line with our hypothesis, melodic context recognition was equally impaired after both LTL and RTL lesion. This suggests a bilateral contribution of the medial temporal lobes in lyric and melody binding. Nevertheless, one important limitation in this study is that melody recognition per se was not examined. This experimental choice was taken to provide a short task that would maximize patients' memory performance. Thus, given the relevance of verbal processing, we chose to focus on the encoding of lyrics and their melodic context. Melodies were always repeated, so that participants could not rely on them to succeed in either lyrics or melodic context recognition tasks. Therefore, the results on melodic context recognition shown by the control group reflect the successful binding of lyrics with the related melodies in this group. However, although the question in the task was related to the correct binding of elements (recognition of the melodic context for a given recognized lyric) and participants were aware that melodies could not be new, the inability to recognize melodies may have resulted in similar performance to the hypothesized deficit in binding with this experimental design. Thus, we cannot exclude that melody recognition deficits may have influenced the failure in melodic context recognition shown by both patients groups. Hence, we will interpret our results with caution, taking this caveat into account in relation with the previous literature.

Deficits in melody processing for patients with RTL excision has been previously shown in perceptual (Zatorre and Halpern, 1993) and memory tasks (Samson and Zatorre, 1991, 1992). For this reason, it is very likely that a deficit in melodic processing in RTL could account for the observed melodic context recognition impairment. Conversely, it has been suggested that the LTL only present deficits in melody recognition when melodies are presented embedded in a song (Samson and Zatorre, 1991). This evidence supports the idea that songs may be initially represented in an integrated way. When the integrated representation is damaged, then access to the elements may be hindered even for the element that is not directly impaired. This interpretation can also accommodate the present deficit of the RTL on lyric recognition. Importantly, melodic context recognition was only evaluated within correct recognized lyric trials. Thus, the lyrics recognition impairment found in LTL is not sufficient to account for the melodic context recognition deficit in this group. These results are in line with previous neuroimaging findings highlighting the role of the left hippocampus on song integration (Alonso et al., 2014a), and support a deficit in binding lyrics with melodies in the LTL patients.

However, it is possible that the implication of right and left damaged regions in binding may not be fully symmetrical. In Alonso and colleagues (2014a), right hippocampal sclerosis patients did not show any significant impairment in adaptation, either for lyrics or for the integration of lyrics and melody. Since melodic recognition deficits have only been reported in patients following a medial temporal lobe resection, it is possible that those deficits are not directly linked to hippocampal damage only. Indeed, Samson and Zatorre (1991) failed to find a direct correlation between hippocampal resection size and melody recognition deficits, suggesting that, unlike binding, melody recognition may not depend on the hippocampus so strongly. However, given our experimental protocol, it is not possible to disambiguate the extent to which deficits shown by RTL, who had full hippocampal removal, are related to melody only and/or binding failure.

In a recent fMRI experiment (Alonso et al., 2014b) we were able to identify the right hippocampus as a key structure for the binding of lyrics and melodies in healthy participants. Although such involvement was more evident when subjects were presented with lyrics and melodies separately than when songs were presented as a whole -like in the present experiment-, simple contrast also pointed out that both right and left hippocampus were more active during successful encoding trials in which unified songs were presented. Therefore, while LTL lesions may have affected binding of songs already at a perceptual level hindering memory binding, we hypothesize that effects shown by RTL patients may reflect a) the involvement of cortical surrounding structures in melody recognition and b) the role of the right hippocampus in memory binding processes.

If an integrated representation would have been formed, then such representation could implicitly facilitate the recognition of the lyrics (Serafine et al., 1984). To look at the particular influence of binding in lyrics recognition, *d'* of lyrics recognition on the different melodic context (original and rearranged songs) were compared in a repeated measures ANOVA. The results showed that lyrics on original songs were better recognized than lyrics on rearranged songs by all participants in line with the integrated processing of songs view (Serafine et al., 1984,1986; Crowder, 1990; Gordon, 2011). Interestingly, this finding confirms that an integrated percept of the song, including the melodic information, may be preserved and used for lyrics recognition despite the deficit found for the explicit recognition of the melodic context. This suggest that although the explicit recognition of the melodic context seems to be impaired in both patient groups, implicit effects of binding on lyrics (item) recognition may be preserved to certain extent. The preservation of implicit effects form a bound representation along with a deficit on the explicit recognition of contextual information, is in line with a previous dissociation found in temporal lobe damaged patients (Shimamura, 1986; Verfaelllie et al., 2012), as well as neuroimaging data showing the implication of the hippocampus in explicit recognition of contextual information, but not in implicit effects of contextual learning (Preston and Gabrieli, 2008).

However, this lack of group differences for this implicit effect is at odds with the perceptual integration deficits found for left hippocampal patients (Alonso et al., 2014a), as well as with the proposed interpretation for the lyric recognition deficit found in RTL patients. Moreover, some studies also suggest a deficit in implicit memory shown by priming in this patient population (Yang et al., 2003). Future studies looking at perceptual integration and memory binding in songs for this particular population are encouraged to reconcile these findings.

Altogether, the study of song memory sheds light on the similarities (Besson and Schön, 2003; for a review see Koelsch, 2013; Patel, 2008; Schön et al., 2005) and differences (Besson et al., 1998; Hébert and Peretz, 2001; Peretz & Coltheart, 2003) between language and music processing. This is relevant from a clinical viewpoint, since it raises the potential development of re-education programs based on the spared function (Baur et al., 2000; Thaut et al., 2008; Simmons-Stern et al., 2012). In particular for patients with temporal lobe epilepsy, differences in the implication of right and left MTL structures in song processing may support the development of neuropsychological test that could be used for the functional assessment of patients. A comprehensive functional assessment of temporal lobe epilepsy patients constitutes an important piece of information for the evaluation of the possible implementation of surgical treatment, and its outcome (Dupont et al., 2010; Djiordjevic et al., 2011; Baxendale, 2008, Helmstaedter et al., 2008). The present results constitute a step forward in understanding the underlying mechanisms for binding lyrics and melodies in the memory for songs, and the expected deficits that as a result of left or right TL lesions.

Conclusion

In sum, we provide novel evidence for the role of left and right medial temporal lobe structures on memory for songs. We support the established deficit of LTL for verbal encoding, as well as for the binding of lyrics with melodies in songs. Furthermore, our data suggest that lyrics recognition can also be affected, although to a smaller extent in RTL patients, supporting a negative influence of the sung presentation of lyrics in memory. Interestingly, an implicit integration effect on lyrics recognition was found in all groups, suggesting that this kind of integration is speared in these patients. Future neuroimaging studies on this particular patient population designed to dissociate lyric, melody and joint contribution of this elements to song memory, may clarify on the issues raised by the present findings.

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Table 1 | Demographic data (Mean ± SD)

Group	Sex (males | females)	Age	Years of education	Musical expertise	BAIS-V
LTL (n=10)	7 | 3	43.2 ± 9.43	12.8 ± 2.25	6.8 ± 7.31	5.49 ± 0.89
RTL (n=10)	4 | 6	48.4 ± 7.56	11.9 ± 1.19	3.35 ± 0.74	5.44 ± 1.25
Control (n=19)	9 | 10	41.42 ± 13.09	13.52 ± 2.09	6.26 ± 3.46	5.19 ± 0.76

Table 2 | Neuropsychological data

Group (*n*)	Age *	FS IQ WAIS-R	RAVLT (∑R1-R5)	Digit span (direct order)
LTL (n=10)	39.8 ± 10.31	91.7 ± 6.94	46.5 ± 4.79	5.7 ± 1.33
RTL (n=10)	44.11 ± 8.17	91.2 ± 10.46	48.6 ± 17.78	5.66 ± 0.86
Normal healthy^	32 ± 9.87		56.25 ± 6.71	

**Age at neuropsychological evaluation; ^ Independent Normal healthy sample*

Table 3 | Stimuli creation for each melody pair and triplet of lyrics

	Lyric 1	Lyric 2	Lyric 3
Melody A	Original song	Rearranged song	New-lyric song
Melody B	Rearranged song	Original song	New-lyric song

Table 4 | Recognition performance

	Lyrics recognition		Melodic context recognition		
	%Correct	d'	%Correct	AUC	p(AUC)
Control	0.97	3.77	0.81	0.89	0.00
	1.00	4.35	0.79	0.80	0.00
	0.94	3.11	0.67	0.67	0.04
	0.92	2.99	0.77	0.80	0.00
	0.92	2.85	0.71	0.70	0.02
	0.99	4.07	0.70	0.68	0.04
	0.92	2.68	0.76	0.78	0.00
	0.99	4.07	0.79	0.86	0.00
	0.96	3.46	0.70	0.68	0.04
	0.97	3.77	0.70	0.74	0.00
	0.96	3.57	0.87	0.86	0.00
	0.97	3.77	0.80	0.81	0.00
	0.97	3.77	0.91	0.91	0.00
	0.94	2.88	0.67	0.72	0.01
	0.97	3.77	0.62	0.63	0.11
	0.90	2.77	0.59	0.65	0.08
	0.94	3.42	0.73	0.76	0.00
	0.90	2.54	0.70	0.73	0.01
	0.96	3.46	0.63	0.62	0.15
LTL	0.79	1.82	0.61	0.53	0.74
	0.53	0.71	0.56	0.58	0.46
	0.68	0.82	0.71	0.76	0.01
	0.82	2.65	0.63	0.63	0.21
	0.69	1.04	0.58	0.50	1.00
	0.63	0.44	0.56	0.62	0.23
	0.71	1.16	0.52	0.50	0.97
	0.84	1.99	0.66	0.62	0.10
	0.81	1.58	0.55	0.58	0.40
	0.90	2.54	0.76	0.73	0.01
RTL	0.85	2.12	0.80	0.83	0.00

0.86	2.08	0.56	0.55	0.59
0.68	2.09	0.48	0.48	0.87
0.90	2.86	0.56	0.57	0.42
0.90	2.64	0.51	0.50	1.00
0.79	1.52	0.58	0.59	0.34
0.94	3.11	0.50	0.54	0.63
0.90	2.88	0.74	0.76	0.00
0.63	1.02	0.64	0.66	0.18
0.94	3.42	0.63	0.73	0.01

Figure 1. Illustration of a left (blue) and of a right (green) median temporal lobe resection (volume before surgery in the upper row, volume after surgery in the lower row) displaying the coronal, the axial and the sagital planes at the level of the hippocampus.

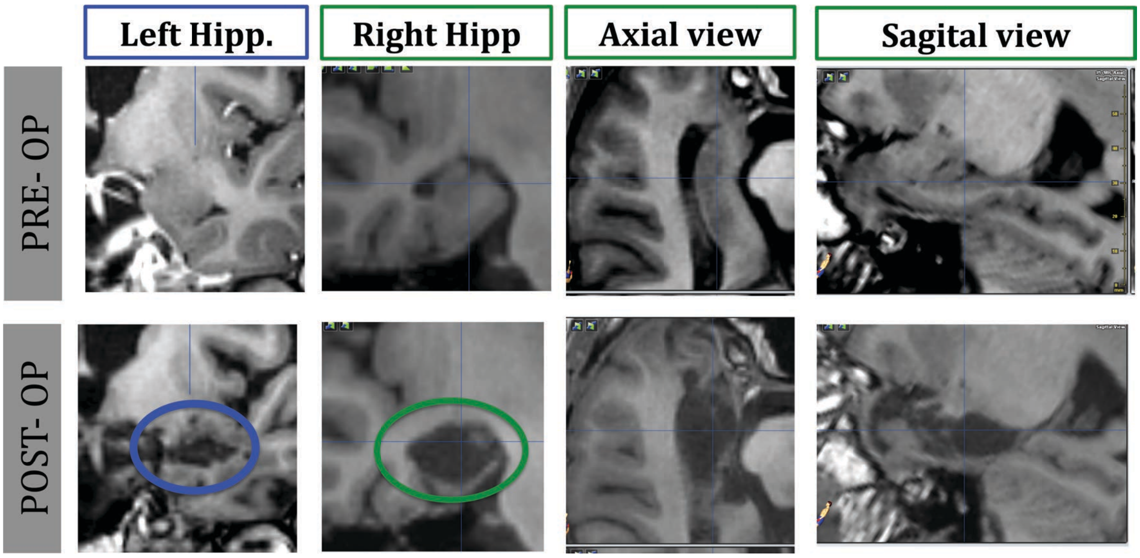


Figure 2. Mean lyrics Recognition (*d' scores*) for the three groups of participants (LTL: left temporal lobe lesion in blue; RTL: right temporal lobe lesion in green ; Control group in orange). *$p < 0.05$; Error bars: Standard Error.

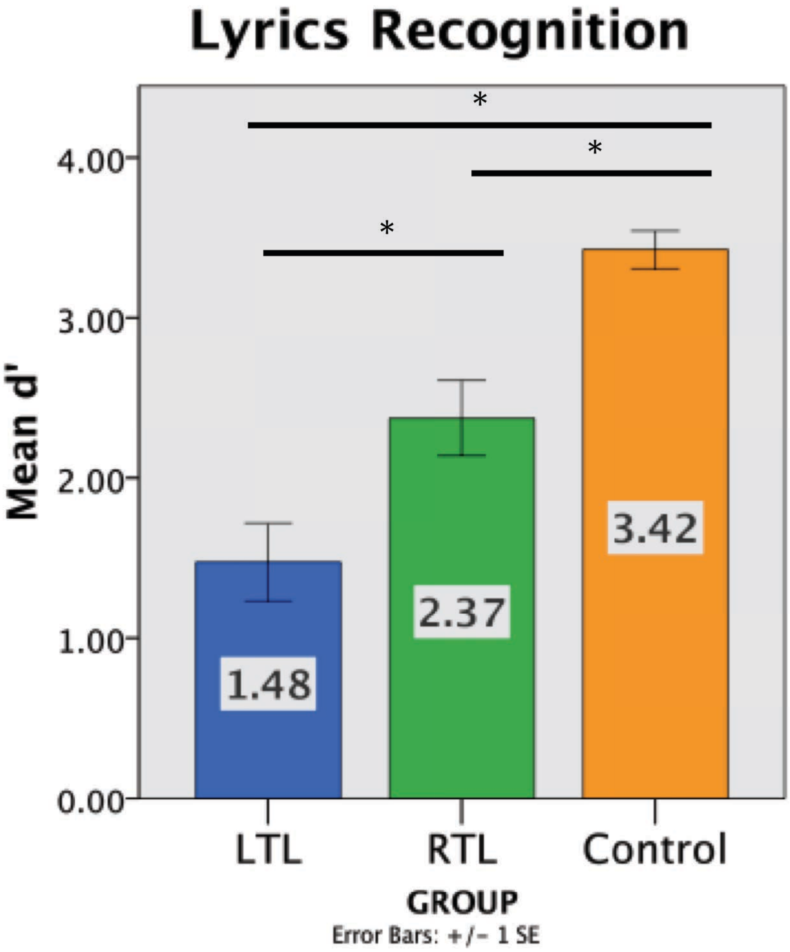


Figure 3. Lyrics Recognition (*d' scores*) and Verbal Memory correlation (as measured by the addition of the 5 successive recognition results in the RAVLT test). Blue circles represent patients with left temporal lobe lesion (LTL) and green circles, patients with right temporal lobe lesion (RTL).* $p < 0.05$.

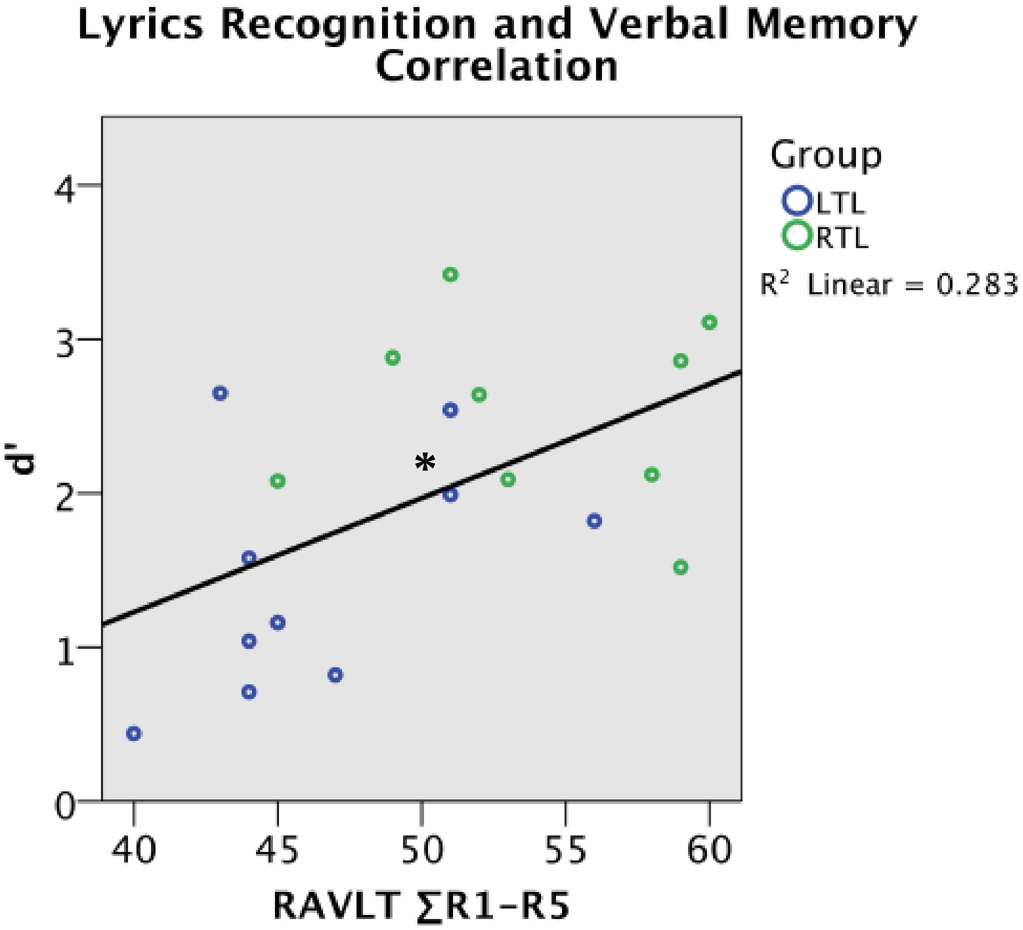


Figure 4. Mean Melodic Context recognition (AUC) for the three groups of participants (LTL: left temporal lobe lesion in blue; RTL: right temporal lobe lesion in green ; Control group in orange). *$p < 0.05$; Error bars: Standard Error.

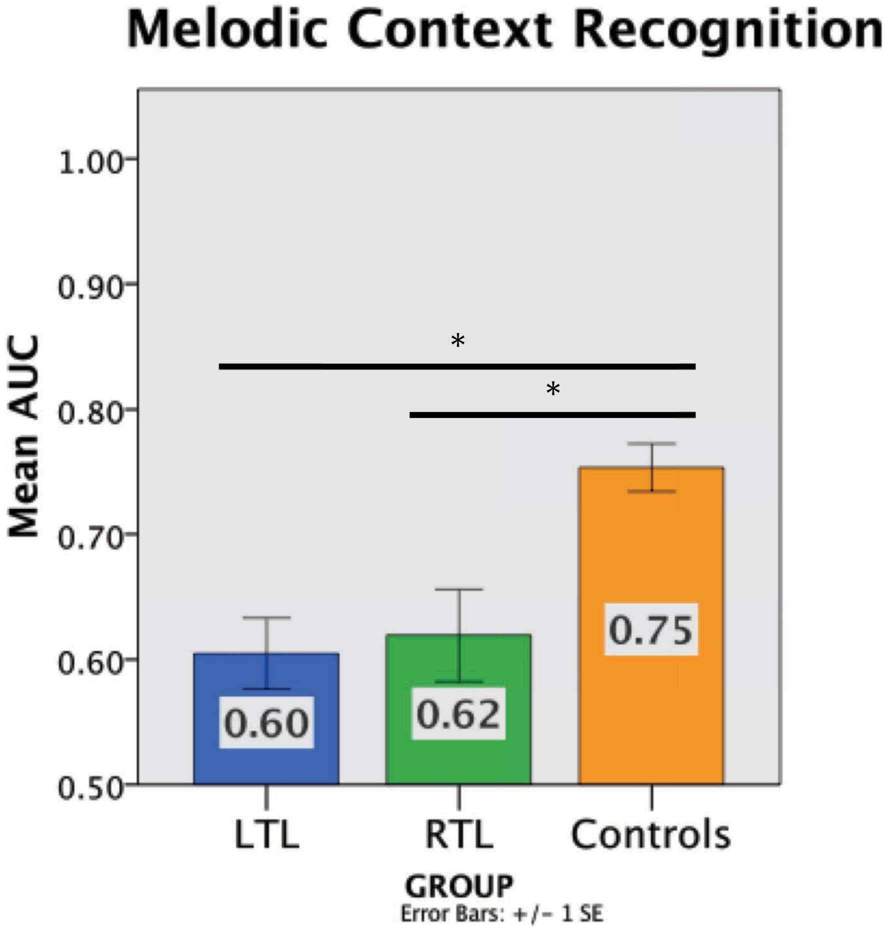
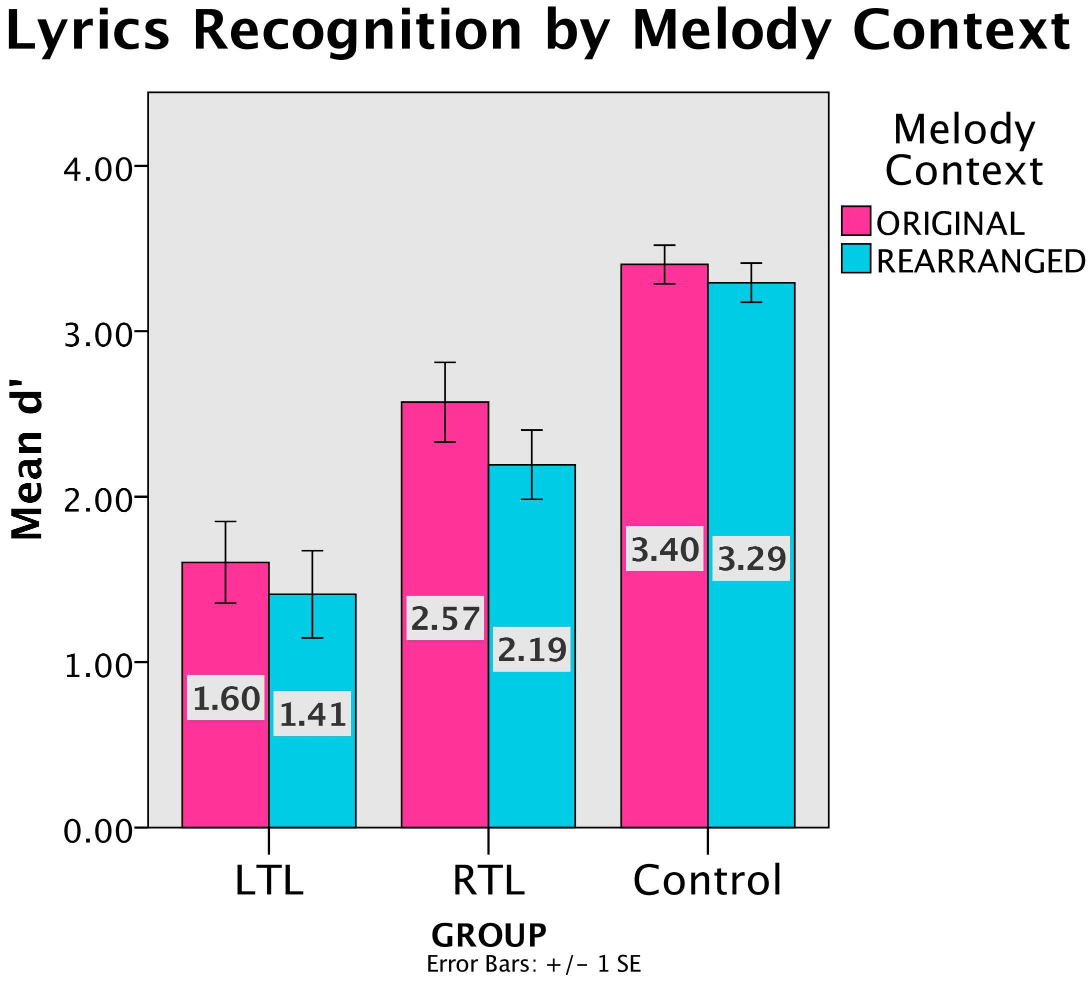


Figure 5. Mean Lyrics Recognition (*d' scores*) by Melodic Context for the three groups of participants. (LTL: left temporal lobe lesion in blue; RTL: right temporal lobe lesion in green ; Control group in orange) *p < 0.05; Error bars: Standard Error.



Chapter 8: General discussion

1. Summary of results

The present thesis has explored the involvement of the hippocampus in binding lyrics and melodies into songs. **Chapter 1** introduced the state-of-the-art on binding from a broad memory perspective. Then, background on music and particularly song processing was provided. Previous research on song production, song perception, song imagery and song memory was presented. This cumulative evidence motivates the core question of this work on the neural substrate of integrative process of lyrics and melodies. The present thesis investigates and articulates this question for the first time in terms of binding. Thus, this work focuses particularly on binding that leads to an integrated memory trace of songs. The involvement of the hippocampus in song binding was investigated using neuropsychology and fMRI methods. Patients with hippocampal lesions as well as healthy subjects participated in these studies.

Study 1 addresses the first question formulated in the introduction "*Can a hippocampus lesion disrupt the integrated percept of new unfamiliar songs?*". **Study 2** addresses both the second "*Is the hippocampus involved in binding lyrics and melodies for the encoding of songs? What other structures may also be involved?*" and third research questions "*Is there a difference between unified and separate presentation of lyrics and melody for song encoding?*". **Study 3** responds to "*How does a temporal lobe lesion including the hippocampus affect song recognition?"*. All of these studies used songs that were manipulated differently to address these research questions. After briefly summarize the main findings of each study, further considerations will be discussed.

The aim of **Study 1** was to assess the modulatory effects of unilateral hippocampal sclerosis on the integration of lyrics and melodies into a conjunctive representation. Neural responses of patients with left or right hippocampal sclerosis were compared to healthy controls using an fMR-adaptation paradigm. Neural adaptation to song repetition was examined as a proxy for song memory formation. It was hypothesized that damage to the hippocampus may disrupt feedback connections to the lateral temporal lobe, and thus preclude the establishment and update of a sensory memory trace. As a consequence, damage to the hippocampus may result in weaker neural adaptation in the superior temporal gyrus (STG). In particular, it was hypothesized that hippocampal lesions might hinder the integration of lyrics and melodies into a unified memory trace (Diana et al., 2007, Staresina and Davachi, 2009; Graham et al., 2010; Shimamura, 2010). The results showed that patients with left hippocampal sclerosis had significantly less adaptation to lyrics as well as to the integration between lyrics and melodies relative to healthy control participants. Thus, a left hippocampus lesion can disrupt the integrated percept of new unfamiliar songs.

Study 2 aimed to examine the cerebral substrate underlying the binding of lyrics and melodies during encoding of songs. Binding of lyrics and melodies took place in two different conditions. In the unified condition, sung lyrics were aurally presented while written lyrics were displayed, and participants were asked to mentally rehearse the song. In the separate condition, elements of the song were presented separately. Melodies sung using the syllable “la” were presented aurally while written lyrics were simultaneously displayed, requiring the participant to mentally combine these two pieces of information into a unified auditory representation of the song and to mentally rehearse and retain it. Binding was addressed by asking subjects to correctly recognize the studied songs (presented exclusively in auditory modality) among other rearranged songs, which contained studied lyrics of one song incorrectly combined with the melody from another studied song. We ensured with an ad-hoc song plausibility test that all participants were able to covertly rehearse a given song and use imagery to create a song from a given melody and written lyrics.

Behavioral analysis using receiving operating curves revealed that all subjects recognized songs in the unified presentation, whereas seven participants were at chance for recognizing songs in the separate presentation. This indicates that the additional cognitive effort required for binding on the separate condition has a behavioral trade-off compared to binding on the unified condition, where the integrated representation was already provided. Overall, our results highlighted the involvement of the right hippocampus along with an auditory-motor network engaged in timing and sequencing processing for binding following the separate presentation of lyrics and melodies. Moreover, the involvement of the left IFG found for binding in the unified condition provides novel evidence for the contribution of this structure to language unification in the specific case of song binding. Responding to our research questions, hippocampus is involved in binding lyrics and melodies for the encoding of songs, and other structures such as the striatum, the cerebellum, and the left IFG are also involved. Importantly, there is a difference between unified and separate presentation of lyrics and melody for song encoding, as these two types of presentation would recruit different networks to achieve successful song encoding.

Study 3 investigates the effects of unilateral temporal lobe lesions, including the hippocampus, on lyric and song recognition. The healthy control group performed better than both patient groups for lyrics recognition. It is worth noting that these differences cannot be attributed to differences in intelligence since patients had normal IQs and the level of education was similar among the three groups. Particularly the LTL group was strongly impaired on lyric recognition, with some participants performing below chance, and thus confirming the left lateralization of lyric encoding. Surprisingly, the RTL group also showed worst recognition of lyrics than controls, although their performance was still significantly better than that of LTL patients. In keeping with our predictions, both LTL and RTL showed a deficit in binding recognition as compared to the healthy control group. However, all participants showed a benefit for lyrics recognition when lyrics were presented with the original melodic context, suggesting an implicit influence of melodic context on lyrics recognition. In sum, a temporal lobe lesion including the hippocampus affect lyric and melodic context recognition to different extents, and particularly regarding the integration of lyrics with their melodic context, explicit recognition of melodic context and the implicit influence of melodic context on lyrics recognition seem to be dissociated.

Based on the combined evidence reported here, a framework for the binding of lyrics and melodies in songs is proposed. Binding occurs at two serial stages: first, at a perceptual stage for the emergence of an integrated representation, and second, during a mnemonic stage where the integrated representation is encoded for its later recognition.

2. Implications and limitations of the thesis

a. The emergence of an integrated song representation

From a physical perspective, song stimuli consist of a sound wave that condenses auditory information – including verbal content – into a discrete signal. Although the psychological interpretation of that signal, under healthy circumstances, will provide the sensation of an integrated auditory object, the song components (mainly melody and lyrics, but also at different level, rhythm (Schulkind, 1999), harmonics, timbre, etc) are processed in disperse areas of the brain. This explains the independence shown by these elements in terms of memory (Halpern and Müllensiefen, 2007; Jerde et al., 2011; Parsons, 2001; Racette and Peretz, 2007), malleability by expertise (Jakobson et al., 2003; Radvansky et al., 1995; Schulze et al., 2011; Tervaniemi, 2009) and also following brain damage (Omar et al., 2010; Peretz and Coltheart, 2003; Peretz et al., 2004; Stewart et al., 2006).

Notably, we focus on the integration of melody and lyrics as they relate to two distinct cognitive domains: Music and Language. These two domains, however, have shown a vast overlap in their use of brain resources (Besson and Schön, 2003; Patel, 2008; Schön et al., 2004). This is not surprising, since both are auditory-based communicational systems that rely on the hierarchical organization of sounds. However, they differ on the sound characteristics upon which their element “identities” and hierarchy rules are based. The frequency of a wave, for instance, will determine pitch, and the length of that sound wave the duration, forming a note. The following notes will relate to it in terms of the particular alignment to a beat (temporal regularity predictions based on durations), as well as the relative frequency distance, that may or may not match the harmonic rules of the western system such that a western listener would cluster the sequence of sounds as a coherent melody.

In the case of language, other variables may be more crucial, for instance the phonological utterances, semantics and syntactic categories of words. Phonemes are culture-dependent sound units of speech, which when combined allow the creation and differentiation of words. Phonemes differ from one another in small variations, produced for instance by the differences in vibration onset (i.e. /p/ and /b/), or other minimal variations on the sound spectrum related for instance to the articulation, or the place of sound production within the vocal tract (i.e. /t/, /k/, /g/). Note that this is cultural-dependent and specific to each language, since the perceptual thresholds, as well as the ability to produce the sounds, will become restricted to meaningful sounds within the native culture. This is illustrated by the difficulties of second language learners to distinguish and learn new sounds that are not present in their native language (Hayes-Harb, 2007).

Perhaps, one of the reasons for which songs are so powerful and widespread, is that they combine both systems to a bound representation, providing aesthetic auditory information that also conveys meaning and emotion. Evidence from behavioral studies has suggested that integration occur both through temporal contiguity and physical feature interaction. The latter mechanism is very relevant to the binding view, since it assumes a conjunctive representation that may be distinct than the individual representation of lyrics and melodies. Thus song listening would elicit a rich integrated percept. During the last decade, few neuroimaging studies have explored the neural substrate underlying song integration as compared to the independent processing of elements (Sammler et al., 2010; Schön et al, 2010; Merrill et al., 2012). These studies agree on the relevance of the left posterior STG/STS in processing an integrated representation of songs. However, binding models that combine computational, animal, neuropsychological and neuroimaging evidence suggest that the MTL is relevant for the encoding of conjunction representations.

The hippocampus has been described as the main structure involved in processing conjunctive representations. Indeed, a growing corpus of literature suggests that hippocampal function is not restricted to episodic memory. Recent studies have shown that the hippocampus is also involved in perception (Lee et al., 2005a, 2005b, 2006; Lee and Rudebeck, 2010b; Schapiro et al., 2012) and also in short term memory (Axmacher et al., 2007; Lee and Rudebeck, 2010a; Rose et al., 2012; Zarahn et al., 2004), as long as there is a need for conjunctive processing (binding), across space and/or time (for a review see Olsen et al., 2012). In this vein, studies supporting this view highlight the functional connectivity of the hippocampus with other neocortical regions, and the feedback and feedforward of information within this network that sustains the emergence of new memories (early from perception throughout encoding and consolidation) and the recognition of old ones (Cer and O’Reilly, 2006; Lavenex and Amaral, 2000; McCormick et al., 2010; Wang and Morris, 2010). This is also in agreement with the EMA memory model (Graham et al., 2010). According to this model, the same anatomically distributed network responds for both memory and perception with some structures being more or less important than others at different stages of the process. Memory arises from a dynamic interaction between neocortical regions, were representations are stored, and MTL function that allows the instauration, consolidation/update and retrieval of the representations.

Building on these ideas, applied on the case of song processing, the first research question of this thesis is formulated *"Can a hippocampus lesion disrupt the integrated percept of new unfamiliar songs?"*. Although integration of lyrics and melody during song perception has been mostly found to rely on posterior areas of the STG, if the hippocampus loop of information is necessary for the emergence of an integrated memory trace, then patients with damage in this structure should show integration deficits. **Study 1** was subsequently designed to quantify the effect of a unilateral hippocampal lesion on neural adaptation for songs.

Study 1 borrowed the fMRI-adaptation paradigm developed by Sammler and colleagues (2010) and applied it with hippocampal sclerosis patients. This particular setting was pertinent to the study of binding features since such repetitions may increasingly lead to the build-up of a memory trace in addition to the well-known perceptual neural priming effects. Furthermore, another strength of this paradigm is that it allows dissociation of the processing of elements within the presentation of unified songs. In other words, lyrics and melodies were always embedded in a song, but the differential variation of one, both or none of the elements allowed for several comparisons to assess specific effects related to each element or to the integration of the song. This approach differs from the **Study 2** where we compared unified to separate song elements presentation.

Healthy participants and patients in **Study 1** showed a similar adaptation profile in response to lyrics and melodies repetitions as shown in Sammler et al., (2010). This general lack of differences between patients and the control group in the main effect indicates that perceptual processes in response to neural adaptation at a cortical level seem to be spared in this clinical population. Nevertheless, areas of adaptation from the patient groups were less extended. Furthermore when compared to the control group, left temporal lobe epilepsy patients (LTLE) showed a significant difference in the left STS whereby LTLE had less adaptation to lyrics than controls. This is coherent with the verbal deficits shown in the neurological assessment (RAVLT forgetting percentages (Sziklas and Jones-Gotman, 2008).

Independent processing of lyrics found in the anterior most parts of the bilateral STG in the healthy group corroborated the general dominance of the verbal component on song processing. Conversely, although none of the patient groups showed a similar independent effect of lyrics, both patient groups showed independent processing of melody in the cerebellum. This finding may be interpreted in terms of compensatory processing, as such activations are not found in the control group. The cerebellum has being previously shown to be involved in the singing network (Callan et al., 2007), and has been related to rhythmic processing (Molinari et al., 2007; O'Reilly et al., 2008; Thaut, 2003). Although at a different stage in the perceptual-mnemonic continuum, this interpretation is in line with results form the GLM on **Study 2**, which showed that successful encoding in the separate condition engaged the cerebellum to a greater extent than in the unified condition. Taking this evidence into consideration, it is possible that patients in **Study 1** may have processed songs in a more segregated fashion than healthy participants, therefore engaging the cerebellum for musical processing.

The main novel contribution of **Study 1** is the highlight of a top-down modulating role of the left hippocampus to support cortical integration, or in other words, the perceptual binding of lyrics and melody. LTLE patients showed reduced adaptation to integration as compared to healthy controls. The results from healthy participants reported in **Study 1** support the role of the posterior STG/STS on the integrative processing of songs. Although previous studies have shown only left lateralized activations, **Study 1** shows novel evidence for a bilateral contribution of this structure, suggesting that the right posterior STG/STS cortex may also support song integration. Note that the described integration process is based on the interaction and therefore differs from the addition of the two elements. This latter idea is underlined by the results on **Study 2**, where the comparison of unified presentation of lyrics and melody in a song against the separate presentation of elements revealed grater activation of the bilateral posterior STG. This evidence suggests that a particular bound representation is formed during perception in this area of the temporal lobe, which is specific to an integrated acoustical signal.

It is unclear, however, if the detrimental processing shown by the LTLE group may be directly or indirectly due to hippocampal malfunctioning. The study of healthy participants have failed to found direct activation or adaptation in the hippocampus during passive listening to song repetitions. However, it is important to note that effects in the hippocampus with fMRI-adaptation paradigms have mainly been reported when the instructions induced an explicit encoding task (Diana et al., 2012; Johnson et al., 2004), a one-back size judgment

(Ganel et al., 2006), or in a human-nature categorization task (Blondin and Lepage, 2005). Thus, it is possible that effects elicited by passive listening may not have been strong enough to be sensitive to MTL function under our statistical threshold, so the direct hippocampal implication at this perceptual stage needs further investigation. Instead, the literature is consistent with the latter indirect interpretation. Damage due to left hippocampal sclerosis hinders feed forward –feedback modulations established between the hippocampus and the cortex. Such loops of information guarantee the updating and integration of information leading to the build-up of a memory trace (Eichenbaum, 2000; McCormick et al., 2010; Nee and Jonides, 2011; Olsen et al., 2012; Shastri, 2002).

One caveat of **Study 1** is that, since it was focused on perceptual aspects, no behavioral data on recognition of songs was collected. That data could have been used to relate the present perceptual effects to encoding deficits. Nevertheless, results from **Study 3** showing recognition impairments on the bound representation of lyrics and melodies in both right and left temporal lobe damaged patients support this interpretation. Overall, these data provide a novel contribution to the current literature, suggesting that the integration shown in healthy participants is tied to the integrity of the medial temporal lobe and its connections with the lateral temporal cortex.

b. Encoding of an integrated song representation

The present thesis proposes the idea that the encoding of a song representation, as an integrated entity, relies on the memory binding of lyrics and melodies. This kind of binding consists of the unification of cortical representations of items, actions, etc. within a spatiotemporal context (Opitz, 2010). In this way, elements of an event are organized to form a coherent experience that is encoded as a single episode. Memory models including the binding function (Davachi, 2006; Diana et al., 2007; Opitz et al., 2010) propose that this process is principally driven by the hippocampus.

In this thesis, the implication of the hippocampus in binding lyrics and melodies is investigated for the first time. Song learning was studied under two conditions; 1) a unified condition with the unified presentation of song elements, and 2) a separate condition with the separate presentation of song elements. Furthermore, the lack of binding studies using auditory stimuli may have hindered the assessment of other brain regions, which may particularly support auditory processing. Hence, other regions of interest that may cooperate with the hippocampus during binding were investigated, including the IFG (Hagoort, 2005; Opitz et al., 2010; Watanabe et al., 2008), the IPL (Kamke et al., 2012; Seghier, 2013; Shafritz et al., 2002), and the basal ganglia (Battaglia et al., 2011; Ben-Yakov and Dudai, 2011; Chan et al., 2013; Nagy et al., 2006; Nenadic et al., 2003; Sadeh et al., 2011). **Study 2** and **Study 3** were designed to shed light on memory binding of songs and address the following research questions: 1) *Is the hippocampus involved in binding lyrics and melodies for the encoding of songs? What other structures are also involved?* (**Study 2**); 2) *Is there a difference between unified and separate presentation of lyrics and melody for song encoding?* (**Study 2**); 3) *How does a temporal lobe lesion including the hippocampus affect song recognition?* (**Study 3**).

i. Unified presentation of song elements: domain-specificity for language binding?

In keeping with our predictions, the unified presentation of songs in **Study 2** elicited activation of the posterior STG and the left IFG. The integrated percept formed in posterior STG, with the feedback influence of the hippocampus as we reported in **Study 1**, may build up a memory trace to be finally bound and encoded in the IFG. On the one hand, binding success revealed by the GLM analysis highlighted the role of the left STG for binding in the unified as compared to the separate presentation. Comparing general activations between the two conditions irrespective of memory performance demonstrated greater involvement of the STG bilaterally when unified song that already contained the integrated representation was provided. As argued by Crowder and colleagues (1990) in the "*physical interaction hypothesis*", one element (lyrics or melodies) exerts subtle physical changes in the other (melodies or lyrics), providing a richer percept than the independent presentation of the two elements (spoken text, melodies without words). The stronger activation in the auditory cortex may represent the superior perceptual richness provided by a unified song, which already provide an integrated representation, as compared to the separated elements. In addition to the literature already described for song perception (Sammler et al., 2010; Schön et al., 2010), recent evidence from electrocorticography further supports the integrative role of the posterior STG for lyrics and music (Sturm et al., 2014).

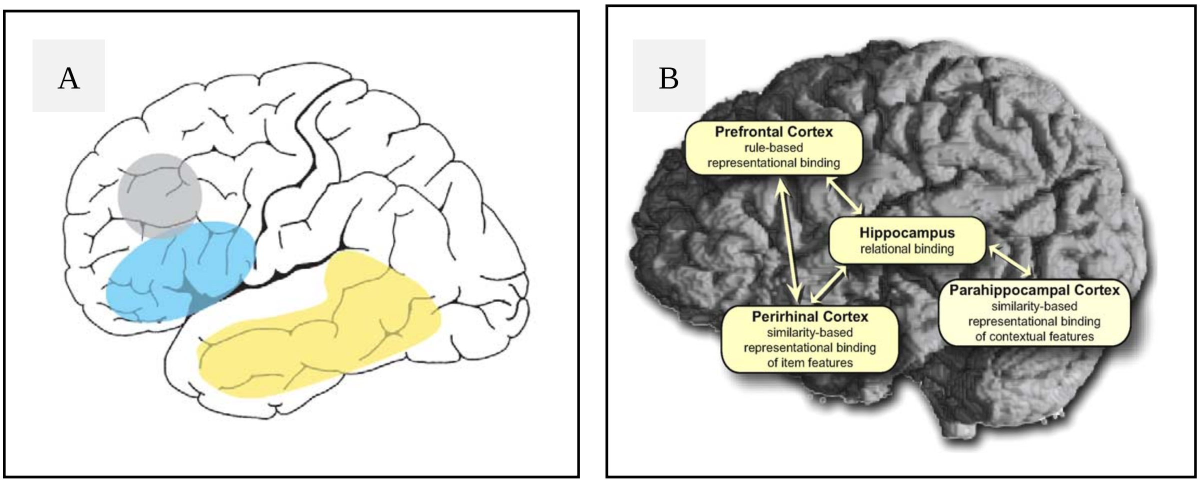


Figure 10. A) Network for the Memory Unification and Control Framework proposed by Hagoort (2005). Yellow in left temporal cortex represents « Memory », blue in LIFG « Unification », and grey in dorsolateral prefrontal cortex (in addition to the anterior cingulate cortex not shown in this illustration) « Control ». **B)** Binding mechanisms mediated by the MTL and the prefrontal cortex as proposed by Opitz (2010). « *The hippocampus is involved in the relational binding of the elements of individual experiences. The surrounding MTL cortex and the PFC extract the common information across multiple experiences forming representational bindings based on perceptual features (MTL) or abstract rules (PFC).* »

On the other hand, the implication of the left IFG in binding songs on the unified condition is in line with the binding account for language processing proposed by Opitz (2010), together with previous studies supporting the role of the IFG on language unification (Hagoort, 2005) and verbal memory (Buchsbaum et al., 2005). In his framework for "language unification", Hagoort (2005) argues that one main differential constraint to language, as opposed to visual integration, resides in the online binding of elements that unfold over different time scales (see also the discussion on time encoding in the following section). This peculiarity justifies the specialization of the left IFG in language unification. The language unification framework proposes that the left IFG supports the hierarchical organization of language across three operational levels of unification: phonological, syntactical and semantic. The novel evidence provided by **Study 2** extends binding in the left IFG of the previously described verbal elements to include melodic features, which are embedded in sung lyrics. This is also in line with the model of speech integration proposed by Hickok and Poepple (2011), where IFG, STG and area SPT interact to support speech integration.

Our results, however, may seem difficult to reconcile with Merrill and colleagues (2012), who argue for a right dominance of verbal integration in the IFG in the context of song processing. In Merrill and colleagues (2012), the contrast revealing integration in the right IFG required the comparison of singing against speech perception (see also Riecker et al., 2000), which may have accentuated the musical contribution in the singing case. Furthermore, this study was designed to measure perception whereas encoding constitutes a different cognitive operation. Studies on singing perception and production have reported a bilateral implication of IFG regions (Brown et al., 2004; Kleber et al., 2007). Note that in our study, when both conditions were analyzed together against baseline, and irrespective of memory, we found activation in both left and right IFG. The right IFG has been previously reported for musical syntactic processing (Koelsch et al., 2005; Sammler et al., 2009), and covert singing (Brown et al., 2004; Kleber et al., 2007). Interestingly, successful binding on the separate condition of **Study 2** revealed right orbital IFG activation. Based on this laterality difference it may be agued here that, although both conditions required covert singing of a song in an integrated form, encoding in the separate condition may initially have relied more on the musical structure, since that was the provided auditory stimulation. Conversely, our results suggest that encoding operations in the unified condition are driven by a linguistic component to a greater extent, and thus rely more on the left than the right IFG. The proposed verbal dominance for encoding is coherent with previous results suggesting additional independent processing of the lyric component in healthy participants (Sammler et al., 2010; Alonso et al., 2014), an effect that has also being shown by comparing tonal and verbal working memory in non-musicians (Schulze and Koelsch, 2012).

Despite this dominant role of the left IFG for binding involving verbal information, Opitz (2010) suggests that the hippocampus may be required for the relational learning of the rules describing relationships between words, such as in artificial grammar learning. Once these rules are learned, they become represented in the left IFG, and consequently the hippocampal activity may no longer be needed (Opitz and Friederici, 2003). Although in **Study 2** we found greater activity in the bilateral hippocampi in the subsequently remembered unified trials compared to baseline, when compared to subsequently forgotten trials the hippocampal contribution to this bound encoding failed to show significance. Notwithstanding, the dominance of IFG in supporting the encoding of this integrated representation does not invalidate the “feedback” contribution of the hippocampus proposed in **Study 1**. Indeed, recognition deficits shown by patients in **Study 3**, in which unified songs were also used, suggest that hippocampus is still required for the binding of lyrics and melodies presented within a song.

ii. Separated presentation of song elements: Encoding information unfolding over time.

A novel contribution of this thesis is to propose that song encoding follows a different mechanism when there is higher degree of separation between song elements to be bound. When no prior integrated representation is provided, the online binding of lyrics and melodies poses greater demands on the hippocampus. Importantly, results from **Study 2** for binding on the separate condition highlight the involvement of the right hippocampus along with an auditory-motor network, which includes the striatum and the cerebellum. The greater involvement of the right hippocampus in binding distal elements here is analogous to that found in the visual domain (Staresina and Davachi, 2009). To this regard, it is worth noting that the work presented in this thesis, and in particular in **Study 2**, provide original evidence to illustrate the binding function of the hippocampus during encoding using auditory stimuli, and the first using musical information.

It is important to note, that although during encoding auditory (melodies) and visual (written lyrics) information was presented, participants were prompted to create a mental auditory representation of song though covert rehearsal. Moreover, reading in this context strikingly depended on the phonological processing, justifying the involvement of auditory mechanisms in addition to visual word recognition and language processing. To further focus on the characteristics of such auditory representation, only aural stimuli were presented during recognition.

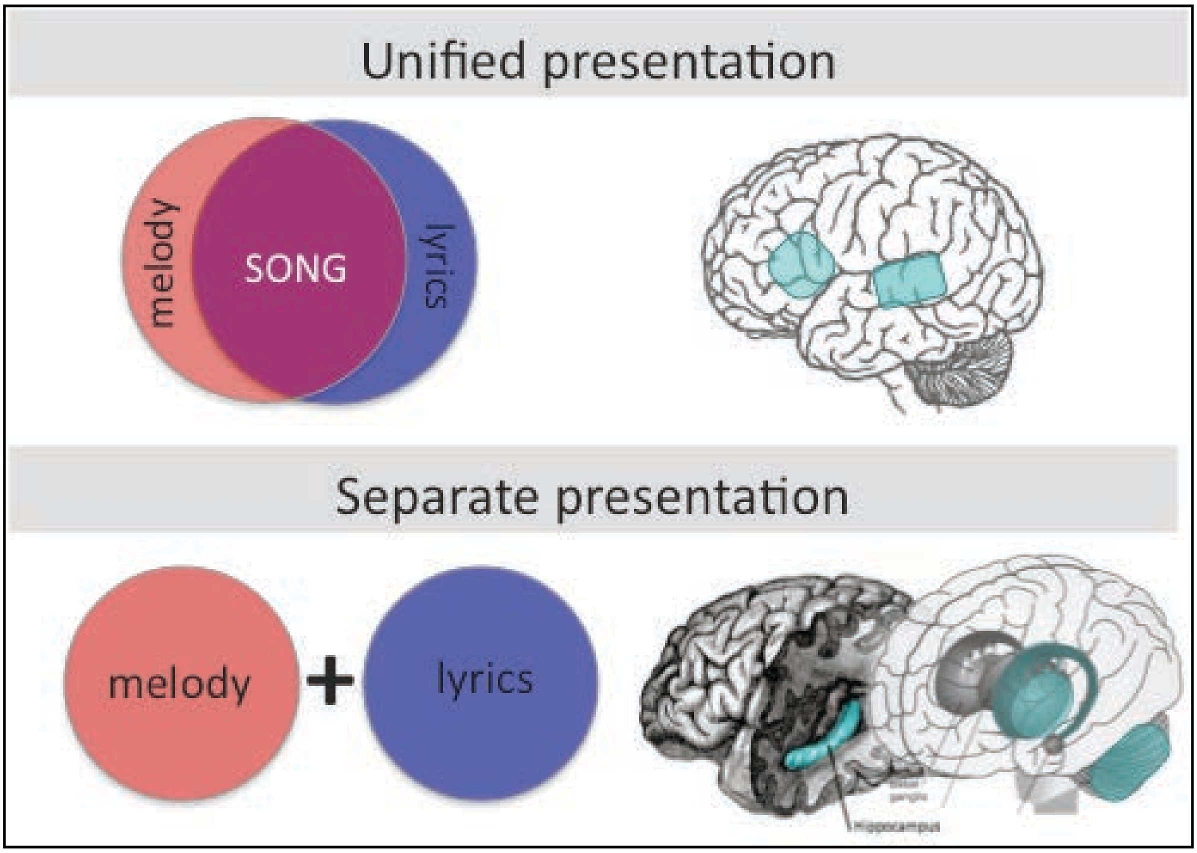


Figure 11. Two distinct mechanisms for binding lyrics and melodies during song encoding. When sung lyrics are provided (unified presentation, upper row), the bilateral posterior STG, together with the left IFG would carry the unification and encoding of lyrics and melodies in an integrated percept. When melody and lyrics are provided separately (Separate presentation, lower row), increasing demands will be posed to the hippocampus to bind these elements into a single auditory object, in cooperation with the basal ganglia and the cerebellum, which will ensure temporal coupling and learning of the sound sequence.

It is worth to keep in mind that STG, IFG, hippocampus, basal ganglia and cerebellum constitute a network for song encoding, which components will be more or less relevant according to the separation between melodies and lyrics, and possibly also depending on the learning stage. Based on this model it could be hypothesized that initial learning of songs will be more dependent on the hippocampus, whereas this bound representation will gradually transfer to a cortical system sustained by the bilateral posterior STG and left IFG.

Interestingly, the results of **Study 2** on successful binding from the GLM analysis reveal activation both in the striatum and the hippocampus only for the separate condition. Both the hippocampus and the striatum have previously been shown to support sequence learning (Albouy et al., 2013; Rieckmann et al., 2010; Schendan et al., 2003), and from a computational perspective, both were identified as “convergence zones” that could bind entities and events through recursive feedback between these areas and the associative cortex (Damasio, 1989). Despite evidence that the contribution of these two structures may rely on distinct processes (Bornstein and Daw, 2012; Myers et al., 2003a, 2003b; Sadeh et al., 2011), the relevance of sequences in binding auditory information may explain activation in both the striatum and the hippocampus. On the one hand, the structural and functional connectivity of the hippocampus can support temporal dynamics, by influencing the synchronization of neuronal firing across brain areas (Eichenbaum, 2014; Lavenex and Amaral, 2000; van Strien et al., 2009). Furthermore, neurons that respond to specific time points within an event have been found in the hippocampus (Eichenbaum, 2013). These neurons, also called time cells, may be responsible for the encoding of temporal properties of stimuli (Eichenbaum, 2014; Shankar and Howard, 2010). On the other hand, the striatum has been described as an internal "pacemaker" (Coull et al., 2011; Ivry and Spencer, 2004; Harrington et al., 1998; Plenz and Kital, 1999) that could account for the temporal context on which sound identity may rely.

Surprisingly, when confidence was considered in combination with accuracy on the parametric analysis, only the striatum was modulated by memory strength. However, when comparing binding in the separate to the unified condition, the right hippocampus and the cerebellum were the main regions with differences in activation. This suggests that these regions bridge the gap between the melodies and lyrics in order to encode a coupled integrated representation.

Broadly, one of the main contributions of this research to the binding view of the MTL function is highlighting the relevance of timekeeping (Treisman, 1963). Although timing may also be relevant in vision to certain extent, it is not surprising that the few studies underlining this idea have used multimodal stimuli (Nagy et al., 2006; Bausenhart, 2014). Despite the idea of temporal contexts was already present in memory models (Dubrow and Davachi, 2014; Ezzyat and Davachi, 2014; Hsieh et al., 2014; Newman and Grace, 1999; Shankar and Howard, 2010), the level of synchronicity behind the concept of timing has not be as strongly considered.

Auditory stimuli identity is dependent on the unfolding of the signal over time. The study of the music domain has provided a wide range of examples where synchronicity becomes indispensable for music perception and production (Farrugia et al., 2012; Janata and

Grafton, 2003; Jakobson et al., 2003; Keller et al., 2014; van der Steen and Keller, 2013). In the case of the study of binding, songs provide optimal stimuli, since timing is crucial to be able to embed the lyrics into the melodic context correctly. This is illustrated by the song plausibility test developed for the inclusion on **Study 2**. In that test, the plausibility of a song given the separate elements was determined by the possibility to match sounds of the melody (musical notes) to sounds of the lyrics (syllables) in a one-to-one basis. The speed of the test (3s to respond) did not allow counting strategies to be used, and instead participants relied on the online coupling of events. Although within the separate condition of **Study 2** songs were always plausible, similar mechanisms were required to warrant the imagery of the song integrating both elements and its encoding.

Therefore, beyond the role of the hippocampus on binding, auditory stimuli characteristics motivate the consideration of the additional contribution of the striatum and cerebellum to song binding. Cerebellum and basal ganglia, which are involved in sequence learning and temporal regularities detection (Bostan et al., 2013; Kotz and Schwartze, 2010; Penhune et al., 1998; Schwartze et al., 2012), were hypothesized to play a role in auditory binding by enhancing learning of related sequences and temporal coupling. Correct learning of song sequence, and temporal coupling of melody and lyrics, may require particularly high timing demands when melody and lyrics are presented separately. Timekeeping and online encoding of temporal information, which especially entails a narrow directionality of elements in sequences (Zatorre et al., 2010), is essential to the identity of auditory information. Although both basal ganglia and the cerebellum have been shown to contribute to time processing at this level, their specific contributions for the encoding of temporal characteristics of stimuli is still under debate (Hazeltine et al., 1997; Malapani et al., 1998; Coull et al., 2011; Merchant et al., 2013).

Studies on auditory or motor imagery recently have become a successful venue to explore timing (Wiener et al., 2010; Keller, 2012; Schaefer, 2014). These types of mental imagery require the representation of fined-grained temporal patterns within which discrete elements may be synchronized and bond. In the binding literature, temporal patterns are articulated as a temporal context. However, in movement or auditory imagery, the representation of this context becomes extremely precise. As an example, the imagery of a song may require a similar duration as the perception of the song, illustrating the identity component attached to rhythmic features (Halpern, 2012).

Some models of time representation accounting for this precision assume the need of an internal timekeeper (Treisman, 1963; Hazeltine et al., 1997; Teki et al., 2012). An internal regular pulse signal may be generated by a timekeeper, setting the pace and the relationship between sound elements (together with motor and other sensory elements) unfolding over time. In this sense, an internal timekeeper may maintain time coding, accumulating structured temporal units, in a similar way than a schema (Buuren et al., 2014) or a virtual spatial grid may subserve spatial coding of a scene (for a review on grid cells see Moser et al., 2008). The existence of an internal flexible but stable timing signal has been suggested to sustain coordinated interpersonal actions (Keller et al., 2014). Notably, music is highly organized in hierarchical levels of time units (Janata and Grafton, 2003). In this way, different patterns of activity in basal ganglia and cerebellum may maintain processing of duration, beat, meter and/or rhythmic patterns (Penhune et al., 1998; Fujioka et al., 2010; Teki et al., 2011b, 2011c; van der Steen et al., 2015).

In the speech literature, both areas have been linked to speech production, the superior cerebellum being engaged in motor preparation and the basal ganglia and inferior cerebellum in execution (Riecker et al., 2005). Interesting, it has been suggested that the cerebellum may have an important role in inner speech (Ackermann et al., 2004). Similarly, activation in the basal ganglia have been reported both for overt and covert singing (Kleber et al., 2007). Studies of patients with cerebellar or basal ganglia lesions have shown functional dissociation between these structures (Shin and Ivry, 2003; Spencer and Ivry, 2005). Shin and Ivry (2003), for instance, have shown a dissociation whereby basal ganglia dysfunction impaired sequence integration whereas cerebellar lesions generally affected sequence association.

On the one hand, studies with patients with cerebellar lesions reveal deficits in perceptual and motor timing (Ivry and Keele, 1989; Malapani et al., 1998; Spencer et al., 2003; Gooch et al., 2010; Harrington et al., 2004), and also in music (Tölgyesi and Evers, 2014). Notably, these deficits seem to lead to a “noisy” signal were durations become inaccurate. This has led some researchers to propose that the cerebellum may be selectively responsible for general duration-based timing (Teki et al., 2012). In this sense, the cerebellum might use the temporal structure of sensory input to generate temporal predictions on sensory events in the near future (O’Reilly et al., 2008).

On the other hand, the basal ganglia have been shown to preferentially contribute to interval encoding relative to cerebellum (Rao et al., 2001; Meck et al., 2008; Harrington et al., 1998). Furthermore, the basal ganglia have been preferentially activated during encoding of perceptual timing tasks (Coull et al., 2008; Rao et al., 2001; Harrington et al., 2004, 2010). Therefore, in contrast to the cerebellum, the basal ganglia have been described to support beat-based timing (Teki et al., 2012). Interestingly, some studies in patients with Parkinson Disease have shown an improvement in gating using external auditory cues (Thaut et al., 1996; McIntosh et al., 1997; Nieuwboer et al., 2007; de Bruin et al., 2010; Benoit et al., 2014). This finding suggests that an external cue processed at the cerebellum may compensate for the lack of an internal “pacemaker” cue in patients with basal ganglia lesions, which may contribute to mitigation of gating problems and improvement of timing skills.

Therefore, this evidence suggests that the cerebellum may be responsible for acuity of perceiving the temporal pattern, which might explain the effectiveness of an external auditory cue for Parkinson patients. Conversely, if the basal ganglia supports the generation of an internal temporal context (like a beat), striatal activity might generate a temporal prediction (Nenadic et al., 2003) within which the precise timing representation, provided by the cerebellum, is contrasted and integrated with other elements, in a cerebello-thalamo-striatal loop. In this way, it could be argued that the cerebellum could affect time perception and encoding more in a bottom-up fashion, whereas the basal ganglia may interact in a more top-down direction. Therefore, the cerebellum may be responsible for the acuity of temporal perception and thus may establish feed-forward temporal predictions (Wolpert et al., 1998; Diedrichsen et al., 2003; O’ Reilly et al., 2008) tied to the external stimulation. In contrast, the basal ganglia may support an internal timekeeper integrative function. Consequently, the functional connectivity between the two would allow the evaluation and encoding of timing features of an event such as a song.

c. Clinical perspectives

To better understand the contributions of the MTL and particularly the hippocampus in binding songs, we recruited patients with lesions in these brain structures to participate in some of the studies presented in this thesis. Two different patient populations have been assessed: patients with hippocampal sclerosis (**Study 1**) and patients with unilateral MTL excision (**Study 3**). In **Study 1**, patients with unilateral hippocampal sclerosis due to pharmacologically resistant temporal lobe epilepsy were compared to a healthy control group in an fMR-adaptation paradigm using songs. Although previous studies in healthy population did not exhibit adaptation in the hippocampus in response to song repetition (Sammler et al., 2010), we predicted a deficit in left hippocampal sclerosis patients based on the binding literature (see **Chapter 1**).

Patients with a left hippocampal lesion showed significant less adaptation to lyrics as well as to the integration of lyrics and melodies, in line with our hypothesis. Although other differences were not significant, both groups of patients had less extended adaptation areas, particularly in the integration contrast. This finding suggests that, the hippocampus may influence cortical activity by providing feedback information (Lavenex and Amaral, 2000; Wang and Morris, 2010). This information seems to be relevant in order to ensure the emergence of an integrated memory trace for songs in line with the EMA memory model (Graham et al., 2010).

In **Study 3**, song recognition performance for healthy participants was compared to that of patients who underwent unilateral surgical removal of MTL structures for the relief of refractory temporal lobe epilepsy (Engel, 1994; Spencer, 2003). Lesions always included amygadala and hippocampus and to a variable extent perirhinal cortex, parahippocampal cortex and temporal pole. Previous results from **Study 2** suggested that, when lyrics were embedded in a melody in the unified presentation of songs, activation was restricted primarily to the left IFG and left STG. According to this study, the hippocampus does not seem to be necessary for the unified encoding of songs, in which case, patients with lesions in that region should not be impaired in lyric and melodic context binding. Nevertheless, previous neuropsychological studies (Samson and Zatorre, 1991) and on results from **Study 1**, support an alternative hypothesis: that bilateral hippocampi may contribute to encoding the bound song.

Therefore, we examined recognition memory for songs in patients with unilateral temporal lobe lesions including the hippocampus to test our hypothesis. Since a deficit in lyric processing was already reported for LTL patients, the experiment was designed to additionally measure memory for lyrics alone. Then in a second step, effects of binding were assessed by looking at both, explicit recognition of the melodic context, and the implicit effect of melodic context on lyrics recognition. As expected, both patients showed recognition impairments for melodic context, reflecting the need of bilateral hippocampi for binding songs. If the IFG was sufficient to ensure binding during encoding of the unified songs, then patients with hippocampal lesions should not exhibit this recognition deficit. Instead, this result provides evidence for an incremental necessity of the hippocampus and the surrounding cortex for such task in line with our hypothesis. Interestingly, when looking at the implicit effect of melodic context on lyrics recognition, an advantage for songs presented in the original context over rearranged songs was found. These results suggest that an integrated representation of the song may implicitly support lyric recognition also in patients, despite the explicit recognition deficit for melodic context recognition. As argue in **Study 2**, songs presented in a unified way provide a rich percept, and based on the physical interaction hypothesis (Crowder et al., 1990), the perceptual representation of sung lyrics would already contain melodic aspects that interact with the verbal information. However, this integrated percept may be independent from the explicit encoding of lyrics and their relation to the melodic context. Thus, it is possible that the left IFG and posterior STG may support the storage of an integrated song representation that could facilitate lyrics recognition, while it is suggested that the lack of either right or left hippocampus may strongly impair the explicit recognition of binding between lyrics and their melodic context.

Interestingly, a deficit in lyric recognition was found in both groups. This deficit was significantly stronger in patients with LTR. Although this is in line with the verbal memory impairment present in left temporal lobe patients (for a review see: Willment and Golby, 2013), the correlation between verbal memory measures and lyrics recognition suggest that when lyrics are merged in melodies, the slight verbal deficits present in some RTL patients may be amplified.

It is worth noting that these results are in agreement with previous work on another set of patients with anterior temporal lobe excision (Samson and Zatorre, 1991). Nevertheless, in that study only 4 songs of each type were presented for recognition, whereas we increase that to 12 songs of each type, improving the robustness of our results. Furthermore, patient's lesions in that study were more extended than in the present study. Excisions in Samson and Zatorre (1991) always included the removal of amygdala the temporal pole and anterior structures of the neocortex, with a variable removal of the Heshl's gyrus, hippocampus, and parahippocampal cortex. Conversely, our patients always included the removal of the amygdala and hippocampus, including only in few cases the temporal pole, as many had follow amygdalohippocampectomy instead of anterior temporal lobe resection, and in any case lesions never affected Helsch's gyrus. Thus, our results are less affected by damage in lateral temporal structures, and more restricted to MTL regions. However, specific volumetric measurements of the resected structures are not reported here. It could have been interesting to quantify a possible correlation of recognition performance with the amount of removal in regions of variable resection across participants, such as the amount of parahippocampal and/or anterior temporal damage. Those correlations could have been valuable to discern the implication of those structures from the role of the amygdala-hippocampal complex.

One limitation in this study is that specific recognition of the melody component was not addressed. This experimental decision was chosen to optimize patients' memory performance, since adding a new condition may have overly complicated the task. In addition to the greater functional value of language, based on **Study 1**, no particular perceptual deficit was found for the melody component. Nevertheless, it may be interesting to elucidate if patients with right temporal lobe lesion may have presented a mnemonic deficit for the melodic component alone, based on the general right dominance of melody processing (Zatorre et al., 1994) and previous work carried out in a similar patient population (Samson and Zatorre, 1991, 1992; Plenger et al., 1996; Wilson and Sailing, 2008).

In both **Study 1** and **Study 3**, patients' results were compared to a healthy control group that matched them in other demographical aspects, including age, gender, years of education, and musical expertise. Thus, these factors do not contaminate the present results. Furthermore, all patients had normal IQ scores, so differences in performance cannot be attributed to general intellectual deficits.

It is important to remind that the main goal of this thesis was to shed light on the regions supporting the binding of lyrics and melodies in memory, and particularly on the role of the MTL. In the neuropsychology field, evaluating patients with selective brain damage to explore brain functions has been a widely extended and insightful research practice (Luria, 1976). However, neuropsychological studies have two well-known disadvantages. The first is the rarity of recruiting patients with a pure uni-structural brain lesion, as most patients may present additional secondary damage or changes in structural connectivity (Besson et al., 2014), which may be directly or indirectly related to the main damaged function. In this sense, we know that temporal lobe epilepsy may negatively affect the functioning of other healthy areas of the patient's brain resulting from epileptic seizures (which can partially account for some of the cognitive performance improvements seen in seizure free patients tested after surgery), and that epilepsy not only damages the hippocampus, but also its connections to other structures (Besson et al., 2014; Centeno and Carmichael, 2014). The second disadvantage is the difficulty in inferring the role and the weight of a targeted damaged structure in a particular function, since lesions may affect more than one isolated region. Although lesion studies allow to test if the damaged area is essential or indispensable to certain cognitive function, it is generally accepted that most cognitive functions recruit a network of regions, and thus, interpretations should be carefully done and always be based on other studies in healthy participants or different patients, which may help to isolate the particular contributions of each region in the network.

Fortunately, the neuropsychological approach has a meaningful advantage that justifies its ongoing use: it has a reversible application of great clinical value. The refinement of behavioral tasks and neuroimaging protocols that isolate a cognitive function, or an element of it, contribute to the development of evaluation tools that could be of use for diagnosis, treatment and rehabilitation of patients with brain damage. In the case of epilepsy, one illustrative example is the current effort of neuropsychologists and neurologists to develop functional neuroimaging protocols that could replace the WADA test (Dupont et al., 2000). The WADA test was traditionally used to predict memory outcome after surgery, and constituted an important piece of information to decide if a patient would benefit from surgery. Additionally, the measurement of music ability may be particularly relevant for the evaluation of both right and left temporal lobe functions as well as for the assessment of brain-damaged musicians (Schulz et al., 2005; Finke et al., 2012; Omigie and Samson, 2014; Wilson et al., 2013).

Hence, the patient studies presented in the current thesis have a prospective goal of contributing to the assessment of temporal lobe epilepsy patients, and other people with memory problems, as for instance, dementia patients, or aging population presenting cognitive decline, yet more work needs to be done. Furthermore, expanding the knowledge of the neural substrate of memory for songs and music binding function may also guide the development of cognitive rehabilitation interventions using songs (Baird and Samson, 2014; Baur et al., 2000; Carruth, 1997; El Haj et al., 2012; Gardiner and Thaut, 2014; Gurr et al., 2014; Irish et al., 2006; Koelsch, 2009; Moussard et al., 2012; Sarakamo et al., 2008; Simmons-Stern et al., 2010,2012; Thaut, 2010; Thaut et al., 2014; Van de Winckel, 2004).

3. Future directions

The present thesis represents a step forward towards the understanding of binding auditory/ audio-visual information, and the implication of the MTL in this process. Although the scope of this work is limited to songs, the described findings highlight the need for further investigation. To complement the neuropsychological studies, a replication of **Study 3** on patients with hippocampal sclerosis (pre-op) or left IFG damage may be informative for particular influences of these regions. Similarly, precise volumetric measurements of patients resections and the correlation of volume removal with memory performance, could also seed light on the interpretation of the current findings. Here, based on the dominance of the lyric component in song processing and the functional relevance of the language domain in the clinic, we have privileged the assessment of the memory for lyrics in the original or rearranged melodic context. Studies measuring all: binding, as well as memory for each element, in a similar manner that **Study 1**, but collecting behavioral data through multiple memory tests would be highly informative. Furthermore, additional behavioral studies assessing recognition and recall of songs on patients with hippocampal lesions may enlarge the range of the assessment applications of the present work. The development of neuropsychological tests in that vein might narrow and improve the evaluative value of these studies.

Taking a connectionist approach, functional connectivity studies on song learning may reinforce and/or refute the cooperative network described here. This thesis predicts that hippocampus, striatum and cerebellum would exhibit high functional connectivity during song learning under separate presentation of lyrics and melodies. Additionally, the IFG, STG/STS and the hippocampus might form an alternative network when songs are presented in a unified form. Moreover, the exploration of the possible transfer from one network to the other, for instance after learning of a song given its separate elements, into the relearning of such song once a integrated representation is acquired, may carry important implications for the use of song learning in a clinical context.

Another logical step forward based on these findings would be to investigate effects of binding in consolidation and retrieval. Looking at the reinstatement of cortical patterns of song representations during recognition with multivariate pattern analysis methods could complement the present thesis by providing a notion of the stored representations of bound information as well as the possible ambiguity of patterns that might lead to false alarms. This technique could also facilitate assessment of independent lyric and melodic reinstatement, which could be informative for the understanding of integration processes.

Although this thesis is focused on songs, the memory field is in need of studies using several types of auditory stimuli and also multimodal experiences. Some suggestions regarding interesting stimuli to explore are binding between voice identity and faces, melody and instrument timbre, musical context and objects or sound and location. Particularly relevant to the present thesis, the study of binding non-verbal features of music can help to better delineate integration characteristics specific to song stimuli, for instance the strong implication of the left IFG or anterior areas of the left STG. Such work is crucial to complete our understanding of binding within and between modalities.

The three studies presented here have used songs from 2- to 3-second durations that contained meaningful sentences. These sequences consisted of 6 to 9 separate sounds. These stimuli were chosen for their ecological validity as a first approach to binding in songs. Based on these results, one possible study may simplify and further control the stimuli by looking at binding at the level of words instead of sentences. Words will have the same syllable length, similar to those used in Schön and colleagues (2010), but to avoid semantic confounds and visual imagery, it may be interesting to use non-words. Then, sequences of non-words and tones could be presented in unified and separate conditions similar to **Study 2**.

In **Study 1**, lyrics and melodies were considered the main song elements. However, from a music cognition perspective, the melody holds at least two distinct components: an interval sequence component, which enchains the different frequencies forming the melodic line, and a rhythmic component, which adjusts those frequencies to a particular beat and rhythmic pattern. The identity of a given melody is therefore attached to both interval sequence and rhythm bond in an integrated representation that constitutes the identity of the melody to be recognized (Jones et al., 1987). The characteristics of fMR-adaptation make it an optimal neuroimaging paradigm to address this question. A two by two block design could be created where blocks contained 6 melodies forming four conditions according to their variation: interval sequence and rhythm are both the same; interval sequence remain the same and rhythm change; interval sequence change and rhythm remain the same; and interval sequence and rhythm change. These stimuli would need to be carefully controlled. For instance, each melody within a block would need to be clearly separated from one another with an irregular temporal gap that could break the temporal regularity of the melody and provide a boundary. Otherwise, perceptual completion between sequences may interfere in the perception when rhythm remains the same since the whole block could be process as one single piece instead of six (indeed, the exploration of the boundary conformation by itself could constitute another study in relation to episodic representation of time). Based on the evidence reviewed and reported in this thesis, neural adaptation in the cerebellum, specific to the rhythmic component can be predicted. Adaptations to the interval sequence component would be expected in turn in the right STG (Zatorre et al., 1994; Zatorre and Belin, 2001). Most importantly, the interaction between interval sequence and rhythm should elicit similar adaptation to our results on songs, on the posterior areas of the bilateral STG/STS, and subsequent memory for the correct integrated representation may elicit hippocampal activation, which in this case could be right lateralized.

Finally, it is well known in the music cognition field that expertise can also influence memory capacity and strategies (Tervaniemi et al., 2001; Seppänen et al., 2007; Groussard et al., 2010; Zuk et al., 2014). Studies investigating professional singers and musicians may allow testing of more fine-grained hypotheses within music memory. For instance, research could assess the neural substrate behind musicians’ ability to bind several melody lines (Fujioka et al., 2005) from different instruments into an integrated representation of a symphonic piece. Furthermore, musicians may also integrate such symphonic representations with procedural memory if they had played it and /or additional memories of the place where it was studied or performed. However, it is important to note that plasticity driven by expertise (Gaab and Schlaug, 2003; Groussard et al., 2010; Herholz and Zatorre, 2012) might also affect the neural substrate supporting such functions, so that generalization from such studies must be done carefully.

Conclusion

This PhD thesis has been realized as part of the EBRAMUS network. The main goal of this interdisciplinary cognitive neuroscience network was to exploit the potential of music to understand brain function and to explore its possible clinical applications.

The aim of the present thesis was to elucidate the role of the MTL on perceptual and memory binding of lyrics and melodies in new song. Behavioral, neuropsychological and neuroimaging methods were combined for this purpose in three original research studies. Altogether, this thesis discusses and provides novel evidence for the role of the hippocampus in binding lyrics and melodies within songs.

Building upon previous results in healthy population (Sammler et al., 2010), **Study 1** showed the implication of the left hippocampus on perceptual binding of lyrics and melodies, suggesting feedback influence of the left hippocampus to the STG/STS to ensure an integrated processing of lyrics and melodies in songs. Overall, **Study 2** highlights the involvement of the right hippocampus in binding lyrics and melodies during song encoding along with an auditory-motor network engaged in timing and sequencing processing for binding following separate presentation of lyrics and melodies. Conversely, the involvement of the left IFG found for binding in the unified condition provides novel evidence for the contribution of this structure in language unification in the specific context of song binding.

From another perspective this results also support the benefit of integrated representations in memory, since memory performance overall was better on the unified than on the separate condition. In particular, **Study 3** supports an integration implicit benefit in lyrics recognition, which seems to be preserved after a hippocampal lesion. However, in line with our predictions, patients with a LTL lesion showed strong lyric recognition impairment together with impairment in explicit binding. The results from RTL patients were harder to interpret given the possible deficit in melodic processing in these patients, particularly for the impairment found in melodic context recognition. Interestingly, although patients with RTL lesion performed significantly better than patients with LTL lesion for lyrics recognition, this patient group presented a mild deficit in lyrics recognition. Lyrics recognition deficits appeared to be related with verbal memory deficits as suggested by the correlation of performance on this test with neuropsychological measures of verbal memory.

The research presented in the present PhD thesis has both theoretical and clinical implications. On the one hand this work demonstrates that music is a powerful tool in basic research to gain knowledge on brain function. In particular, the approach applied here highlights the necessity of accounting for modality specific constrains in memory models. Here, we discuss and provide novel evidence for the role of the hippocampus in binding lyrics and melodies within songs. Nevertheless, in light of these results, other structures such as the IFG, basal ganglia and the cerebellum seem to be relevant for binding auditory information in time and should be explored in more detail in future studies. Further investigations on the effects of an hippocampal lesion on song binding, or using different types of auditory stimuli, as for instance voice identity or instrument timbre with melody will be required to complete our understanding of binding auditory information within and between modalities.

On the other hand, these findings carry insightful clinical implications that contribute to understand the possible benefits of music, and particularly songs, in boosting cognitive health among clinical populations with memory problems, such as Alzheimer's disease, certain types of epilepsy or even healthy aging. For instance the laterality differences found for left and right damaged patients provides meaningful neuropsychological testing tools, which can be particularly useful for the assessment of musician patients (Wilson et al., 2013; Omigie and Samson, 2014). All in all, the improvement of life expectancy in Europe and other developed countries, face the challenge of an aging population. A higher prevalence of degenerative diseases generally characterized by memory loss (i.e. Alzheimer’s and other dementias) has been foreseen. Therefore, in addition to the potential of music as a tool to explore and provide mechanistic models of neurocognitive function - as we have demonstrated in this thesis-, understanding the brain basis of musical processing represents one step further in the development of non-pharmacological therapies that could contribute to slow the deterioration of memory, and above all, to improve people’s welfare.

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Appendix · A | List of publications and presentations.

Publications

- **Alonso, I.**, Sammler, D., Valabrègue, R., Dinkelacker V., Dupont, S., Belin, P. & Samson, S. (2014) Hippocampal sclerosis affects fMR-adaptation of lyrics and melodies in songs. *Frontiers in Human Neuroscience, 8,* article 111. doi: 10.3389/fnhum.2014.00111
- **Alonso, I.**, Davachi, L., Valabrègue, R., Lambrecq, V., Dupont, S., & Samson, S. (in preparation) Neural correlates of binding lyrics and melodies for the encoding of new songs.
- **Alonso, I.**, Lambrecq, V. Dupont, S. & Samson, S. (in preparation) Binding lyrics and melodic context in memory for songs following unilateral temporal lobe excision including the hippocampus.

Talks and Seminars

2014

- **Alonso, I.**, Davachi, L., Valabrègue, R., Dupont, S. & Samson, S. (November) Singing in the brain: neural correlates of auditory binding of lyrics and melodies. Society for Neuroscience Annual meeting, Washington D.C., US. (**Nanosymposium**)

2013

- **Alonso, I.** (20th -22nd September) Memory for songs: binding lyrics and melodies. EBRAMUS International Conference "New perspectives for stimulating cognitive and sensory processes". Pavia, Italy. (**Talk**)
- **Alonso, I.** (June) La canción de la memoria: música y cerebro, Proyecto pedagógico La Barraca, Asociación Scherzi Musicali, Conservatorio Municipal Dionisio Díez, Miranda de Ebro, España. (**Divulgation seminar**)
- **Alonso, I.** (May) La canción de la memoria: música y cerebro, Seminaires du Comité de Culture, Colegio de España, Cité Universitaire International de Paris, Paris, France. (**Divulgation seminar**)

- **Alonso, I.** (January) Auditory binding: imaged encoding of songs. Music in the rehabilitation of patients with memory and learning deficits workshop, Lille, France. (**Talk**)

2012

- **Alonso, I.** (October) Neural priming of songs: the relationship between lyrics and tunes. Donders Discussions 2012, Nijmegen, The Netherlands. (**Talk**)
- **Alonso, I.** (30th April) Música y Cerebro. Conservatorio Superior de Música de Oviedo Eduardo Martínez Torner. (**Divulgation seminar**)
- **Alonso, I.** (27th April) Música y Cerebro. University of Oviedo, Psychology faculty. (**Talk**)
- **Alonso, I.** (24th April) The effect of Temporal Lobe Epilepsy in the relationship of lyrics and tunes: an fMRI-adaptation study with songs. IMHSD University of Edinburgh, UK. (**Talk**)

Poster presentations

2015

- **Alonso, I.**, Lambrecq, V. Dupont, S. & Samson, S. (March) Memory for songs following unilateral temporal lobe resection. Cognitive Neuroscience Society Meeting, San Francisco, US.

2014

- **Alonso, I.**, Lambrecq, V. Dupont, S. & Samson, S. (May) Memory for songs following unilateral temporal lobe resection. The Neurosciences and Music V conference, Dijon, France.

2012

- **Alonso, I.**, Sammler, D., Valabrègue, R., Dupont, S., Belin, P. & Samson, S. (July) The effect of unilateral temporal lobe lesion during passive listening to songs: an f-MR-adaptation study. FENS Forum 2012 in Barcelona, Spain.

2011

- **Alonso, I.**,Vanhouke, E., Filoche, E., Samson, S. (December) Memory for music and words by manipulating emotional dimensions. Journées de Jeunes chercheurs en Audition, Acustique musical et Signal audio, Rennes, France.
- **Alonso, I.**, Sammler, D., Valabrègue, R., Dupont, S., Belin, P. & Samson, S. (June) The role of the medial temporal lobe in encoding unfamiliar songs: An fMR-Adaptation Study. Poster session at The Neurosciences and Music IV conference, Edinburgh, Scotland, UK.

Appendix · B | Tangential scientific work.

Emotional memory for musical excerpts in young and older adults.

Alonso, I., Dellacherie, D., Samson, S. (2015) Emotional memory for musical excerpts in young and older adults. *Frontiers in Aging Neuroscience*, *7*, 23. doi: 10.3389/fnagi.2015.00023.

Music in the rehabilitation of patients with memory and learning deficits. International workshop - Lille 2013.

See : https://prezi.com/gcssjfjzu3m5/music-in-rehabilitation-of-memory-and-learning-deficits/

Emotional memory for musical excerpts in young and older adults.

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Emotional memory for musical excerpts in young and older adults

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The emotions evoked by music can enhance recognition of excerpts. It has been suggested that memory is better for high than for low arousing music (Eschrich et al., 2005; Samson et al., 2009), but it remains unclear whether positively (Eschrich et al., 2008) or negatively valenced music (Aubé et al., 2013; Vieillard and Gilet, 2013) may be better recognized. Moreover, we still know very little about the influence of age on emotional memory for music. To address these issues, we tested emotional memory for music in young and older adults using musical excerpts varying in terms of arousal and valence. Participants completed immediate and 24 h delayed recognition tests. We predicted highly arousing excerpts to be better recognized by both groups in immediate recognition. We hypothesized that arousal may compensate consolidation deficits in aging, thus showing more prominent benefit of high over low arousing stimuli in older than younger adults on delayed recognition. We also hypothesized worst retention of negative excerpts for the older group, resulting in a recognition benefit for positive over negative excerpts specific to older adults. Our results suggest that although older adults had worse recognition than young adults overall, effects of emotion on memory do not seem to be modified by aging. Results on immediate recognition suggest that recognition of low arousing excerpts can be affected by valence, with better memory for positive relative to negative low arousing music. However, 24 h delayed recognition results demonstrate effects of emotion on memory consolidation regardless of age, with a recognition benefit for high arousal and for negatively valenced music. The present study highlights the role of emotion on memory consolidation. Findings are examined in light of the literature on emotional memory for music and for other stimuli. We finally discuss the implication of the present results for potential music interventions in aging and dementia.

Keywords: emotion, memory, consolidation, valence, arousal, music, aging

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Introduction

It has been well established that emotional events are better memorized than non-emotional events (for a review see LaBar and Cabeza, 2006; Bennion et al., 2013; Talmi, 2013). Listening to music can evoke powerful emotions (Juslin and Västfjäll, 2008; Koelsch, 2010; Cochrane et al., 2013) that can subsequently influence memory. A growing number of studies suggest that music can produce durable memories in normal as well as pathological aging, and that this could be due in part to emotion (Bartlett and Snelus, 1980; Bartlett et al., 1995; Schulkind et al., 1999; Janata et al., 2007; Samson et al., 2009; Simmons-Stern et al., 2010).

To investigate the effects of emotion on memory, researchers have applied emotional memory paradigms, which compare memory for stimuli with different emotional characteristics. Most studies in emotional memory have adopted a dimensional approach that characterizes emotions in a graded continuum space that is defined classically by two main dimensions: arousal and valence (Russell, 1980; Bradley, 1994). On the one hand, arousal provides a representation of excitement and calmness. High-arousing stimuli have generally showed a mnemonic advantage over low-arousing stimuli (for a review, see Dolcos and Denkova, 2014). High arousal has been shown to enhance memory both at the initial encoding of events, by boosting attention, as well as during consolidation (for a review see Hamann, 2001; Mather and Sutherland, 2011). On the other hand, valence refers to the positive or negative emotion of the stimulus. In non-musical domains, both positive and negative stimuli have shown to enhance memory as opposed to non-emotional stimuli (Hamann et al., 1999; Dolcos and Cabeza, 2002). Nevertheless, a number of studies speak to a benefit in recognition of negative events as compared to positive events, for words (Inaba et al., 2005) and pictures (Mickley and Kensinger, 2008) suggesting an effect of valence on memory favoring negative stimuli (for a review, see Kensinger, 2007).

Most importantly, it may become difficult to interpret the results of studies that look only at one dimension without controlling for the other. For example, negative stimuli have been regularly described to be better encoded than neutral stimuli (Inaba et al., 2005; Murty et al., 2009), but it is worth noting that such stimuli may also be more arousing overall (Ortony et al., 1983; Denburg et al., 2003; Feng et al., 2014, for a review see Mather and Sutherland, 2009). Looking at both valence and arousal dimensions, Adelman and Estes (2013) have shown that the memory benefit for emotionally valenced words, whether positive or negative, over neutral words may be independent of arousal. The necessity to test the conjoint effect of valence and arousal is further supported by neuroimaging studies, which suggest that arousal and valence influence memory through two distinct neural mechanisms (Dolcos et al., 2004; Kensinger and Corkin, 2004; for a review see Murty et al., 2010; Dolcos et al., 2012).

However, it has been shown that effects of arousal and valence on memory may interact (Libkuman et al., 2004; Jefferies et al., 2008; Mickley Steinmetz et al., 2010a; Citron et al., 2014). An interaction between valence and arousal has been shown, for instance, in patients with amygdala lesions (Berntson et al., 2007), whose recognition of negative scenes was modulated by arousal levels, without an effect of arousal on the recognition of positive scenes. This combined evidence highlights the importance of accounting for both emotional arousal and valence of the stimuli to properly assess the independence and/or the interaction of these emotional effects (Kensinger, 2008; Mickley Steinmetz et al., 2010a; Adelman and Estes, 2013; Feng et al., 2014; Gallant and Yang, 2014; for a review see Levine and Pizarro, 2004; Libkuman et al., 2004; Kensinger, 2009; Mather and Sutherland, 2009).

Emotion can influence memory both at encoding and during consolidation (Hamann, 2001). First, arousal (Bradley et al., 1992; MacKay et al., 2004; Mickley Steinmetz et al., 2010b) and valence (MacKay et al., 2004; Thomas, 2006; Talmi et al., 2007) may boost attention during encoding, facilitating the initial processing of information, and consequently, enhancing immediate recognition. As it has been previously discussed, high arousal and negative valence may enhance encoding, resulting in better immediate recognition for these stimuli as compared to low arousing and positively valenced stimuli respectively (MacKay et al., 2004; for a review see Kensinger, 2007). Second, emotion can further modulate memory after encoding through consolidation. Memory consolidation consists of the stabilization of new memories, whereby some memory traces are strengthened to be later retained and other memory traces will become weaker and be subsequently forgotten (for a review see McGaugh, 2000). The reorganization process occurring through consolidation requires a delay and is mainly driven by hormonal release (Buchanan and Lovallo, 2001), being particularly boosted by sleep. Effects of emotion on consolidation are therefore captured by recognition tests with longer delays, particularly after 24 h (Wagner et al., 2005, 2006; Hu et al., 2006; Payne and Kensinger, 2011; Bennion et al., 2015). Although both arousal and valence have shown to affect the initial encoding of events, evidence for long-term effects of emotion on memory has traditionally highlighted the influence of arousal (Bradley et al., 1992). Several lines of evidence suggest that arousal can critically modulate consolidation (Kuhlmann and Wolf, 2006; for a review see Hamann, 2001; Mather and Sutherland, 2011), with high arousing stimuli facilitating delayed recognition. Relatively few studies have investigated the role of valence on consolidation showing an enhancement for negatively as compared to positively valenced stimuli after at least 24 h delay (Kensinger et al., 2007; Waring and Kensinger, 2009). However, this remains an open area of research.

In the musical domain, few studies have investigated emotional memory (Eschrich et al., 2005, 2008; Samson et al., 2009; Aubé et al., 2013; Vieillard and Gilet, 2013; Altenmüller et al., 2014). Eschrich et al. (2005) manipulated valence (positive to negative), arousal (very arousing to very pacifying) and emotional strength (very strong emotions to no emotions) of Bach piano music excerpts to address the effects of emotion on memory for music. Memory for the studied excerpts was tested 2 weeks after encoding with a remember/known paradigm. Arousal was shown to be the main dimension affecting recognition, with better memory for very arousing than for very pacifying Bach excerpts. To further explore these effects, another study was conducted (Eschrich et al., 2008) presenting emotional film music excerpts with a relatively long length of 20–30 s. Similarly to the previous study, the authors manipulated valence, arousal and emotional intensity dimensions, although valence ratings only ranged from less positive to very positive, thus excluding the assessment of negative emotions. Participants were split into two groups with different incidental encoding tasks: an emotional rating task promoting deep encoding or a time estimation task promoting more shallow encoding. Then, the next day, stimuli were presented again to reinforce consolidation. On the third day, participants were given a surprise old/new recognition test. No differences were found between the deep and the shallow encoding groups. In contrast with the previous study (Eschrich et al., 2005), the results did not confirm the effect of arousal or of emotional intensity on recognition but revealed an effect of valence on recognition, with better memory for very positive music than for less positive excerpts. However, in a recent neuroimaging study, Altenmüller et al. (2014) failed to replicate this behavioral recognition benefit for very positive over less positive music following the encoding of film excerpts including some of the same excerpts from Eschrich et al. (2008) and few similar new excerpts. Furthermore, the lack of negative excerpts in these two studies limits the interpretation of the results that do not seem to support findings from non-musical domains, which indicate that negative objects may be better recognized than positive objects (for a review see Kensinger, 2007). Thus, although high positivity of musical excerpts seems to enhance recognition, it remains unclear whether high negativity of excerpts could have also provide an advantage for music memory in healthy young adults.

Other studies on emotional memory for music have used computer-generated midi musical excerpts recorded with a piano timbre (Samson et al., 2009; Aubé et al., 2013; Vieillard and Gilet, 2013). These stimuli were created and validated to express happy, fearful, peaceful, or sad emotions (Gosselin et al., 2005; Vieillard et al., 2008). In a first study (Samson et al., 2009), the participants listened to the stimuli four times and recognition was incidentally assessed after 24 h delay. Recognition was higher for happy and fearful than for sad and peaceful excerpts. As pointed out by the authors, better recognition of scary music seems to be attributed to a confounding factor (higher discriminability between fear stimuli as compared to the other types of stimuli). However, successful recognition of happy music suggests efficient consolidation of either high arousing or positively valenced stimuli. More recently Aubé et al. (2013) conducted a series of experiments focusing on the impact of emotion expressed by music on immediate recognition in young adults. By using short segment of music (1.5 s), the authors confirmed better recognition of both happy and fearful excerpts above the other categories indicating an effect of arousal in recognition memory. However, when the number of events was kept constant (instead of the duration of excerpts) recognition memory enhancement was obtained only for the fearful excerpts. The authors interpret these results as an advantage for threat-related processing as compared to the other emotional categories, although the higher discriminability of target and foils of the fear stimuli previously noted may partially explain the memory results.

All in all, although an effect of arousal on delayed recognition has been suggested (Eschrich et al., 2005), subsequent studies have not succeeded to disentangle the effect of arousal from the effect of valence (Samson et al., 2009; Aubé et al., 2013). Furthermore, the effect of valence on recognition remains controversial, being unclear whether negative (Aubé et al., 2013) or positive valence music (Eschrich et al., 2008; Samson et al., 2009) may be better recognized.

Moreover, and of great relevance for the present study, effects of emotional memory may vary with aging (for a review see Mather, 2004). Aging is typically associated with memory decline, and weakened consolidation (Scullin, 2013). However, it seems that older adults are not only generally less efficient than the young, but also use different strategies to retain items and events (Carstensen and Turk-Charles, 1994; Gallant and Yang, 2014; for a review see Mather, 2004). A memory advantage for positive stimuli over neutral or negative stimuli, together with diminished processing of negative stimuli has been frequently reported in aged (Charles et al., 2003; Mather and Carstensen, 2005; Mather and Knight, 2005; Thomas, 2006) as compared to younger adults (for a review see Mather, 2006; Reed et al., 2014). Such an emotional bias in aging has been described for words (Leigland et al., 2004; Kensinger, 2008) (for contrasting results see Grühn et al., 2005), pictures (Charles et al., 2003), as well as for emotional processing in music (Lima and Castro, 2011; Vieillard and Gilet, 2013).

In contrast, few studies suggest that valence effects on consolidation do not differ with aging, either when showing an advantage for negative stimuli as compared to positive stimuli (Comblain et al., 2004; Kensinger et al., 2007; Kensinger and Schacter, 2008; Waring and Kensinger, 2009) or vice versa (Denburg et al., 2003). Regarding the effect of arousal, enhancing recognition of high arousing events has been frequently demonstrated in aging (Kensinger et al., 2002; Otani et al., 2007; Kensinger, 2008), even after a 24 h delay (Waring and Kensinger, 2009). Although general consolidation deficits have been described in older adults (Cherdieu et al., 2014), it is possible that arousal may exert a compensatory role, which may result in greater benefit of high arousing events after a delay for older than for young adults. Such an interpretation has recently been challenged in a study investigating immediate and 24 h delayed memory of emotional pictures in aging (Leal and Yassa, 2014). Results in this study suggest that whereas older adults (as opposed to younger adults) benefit from high arousing pictures for immediate recognition, emotional memories in the older group are dramatically forgotten after 24 h. This discrepancy between findings underlines the need to take immediate and delayed recognition into account, in special for studies comparing young and older adults.

To our knowledge, only one study has addressed the effects of aging on emotional memory for music (Vieillard and Gilet, 2013). This study compared immediate memory recognition for music in young (19–24 years old) and older (60–84 years old) adults using the emotional short computer-generated midi musical excerpts previously described (Gosselin et al., 2005; Vieillard et al., 2008). Although an overall memory advantage was found for young adults as compared to older adults, all participants showed a recognition advantage for fearful excerpts as compared to the other music stimuli, similar to the results reported by Aubé et al. (2013) for young adults. However, memory performance of all participants was very low. This floor effect might have hindered the sensitivity for other possible emotional memory differences. In addition, the lower false alarm rates for the fear stimuli as compared to the other emotional stimuli in this study further reflects the issue of the higher discriminability of fear excerpts (Samson et al., 2009) previously discussed. Differences in the emotional responsiveness to music were also found, whereby older adults showed lower discriminability of happy excerpts together with a decrease in their responsiveness to sad and scary music as compared to young adults.

In the present study we addressed the effect of normal aging on emotional memory, assessing immediate and delayed recognition of musical excerpts by manipulating emotional dimensions, arousal and valence, in young and older adults. First, we predicted a general effect of age on recognition of emotional music, with a reduced recognition performance overall for older adults. Regarding the effect of arousal, we hypothesized a benefit on memory performance for high arousal excerpts in both groups. Furthermore, we expected that arousal would not only benefit immediate recognition but also compensate weakened consolidation in aging. Therefore, we predicted a benefit of high over low arousing stimuli in the delayed recognition test that will be greater for old than for young adults. However, based on previous studies on aging and emotional memory in other domains, we expected an interaction effect of age and valence to be manifested by a bias toward worst recognition of negative excerpts in the older adult group but not in the young group.

Materials and Methods

Participants

Thirty native French speakers were included in this study. Two different groups were conformed according to age, a group of 15 young adults (mean age = 22 ± 1.8, ranging from 18 to 25 years; 8 female; years of education = 14.2 ± 2.11, ranging from 9 to 16 years) and another group of 15 older adults (mean age = 75.27 ± 8.54, ranging from 63 to 92 years; 10 female; years of education = 12 ± 4.42, ranging from 6 to 20 years). All participants were right handed as determined by the Edinburgh Inventory (Oldfield, 1971). Existence of psychiatric or neurologic conditions, as well as the current intake of any treatment affecting memory was taken as exclusion criteria for both young and old adults. Only participants with scores within the normal range on the Profile of Mood State (POMS) test for anxiety, depression and tiredness, were included in the sample to ensure that none of the participants had mood disorders that could interfere with emotional processing. Both young (mean ± SD = 4.47 ± 2.17) and older (mean ± SD = 3.80 ± 1.61) participants were non-musicians as attested by the Music Expertise Test (Ehrlé, 1998). All older adults had Mini-Mental Status Examination (Folstein et al., 1975) scores greater than 28 (mean ± SD = 29.27 ± 0.88), ensuring that their cognitive function was normal. The two groups did not differed on their level of education ($t = 1.74$; $df = 20.06$; $p = 0.097$). All participants have signed informed consent and the study was carried out following the declaration of Helsinki principles.

Stimuli

Musical stimuli consisted of 48 symphonic excerpts of 5 s. duration (± 1 s fade in fade out) taken from different symphonies written by composers between 1830 and 1954. We selected this period for its particular emphasis in emotional expression, and chose to use existent symphonies to provide more naturalistic stimuli. However, to control the effect of familiarity, we excluded the most famous composers and symphonies of this period.

We used a 2 by 2 design where two dimensions, valence (positive or negative) and arousal (high or low), were crossed creating 4 different emotional combinations of valence and arousal: positive and high arousing (V+A+), positive and low arousing (V+A−), negative and high arousing (V−A+) and negative and low arousing (V−A−). Four sets of excerpts were selected for each emotional combination (making 16 sets of excerpts) based on emotional agreement ratings in an independent pilot study. In this pilot study, 232 excerpts were rated in terms of valence (positive, negative), and arousal (high, low). One hundred seventy five participants were asked to rate a pseudo-randomized subset of 33 out of the 232 excerpts in terms of valence (positive, negative) and arousal (high, low). Excerpts with the higher percentage of agreement on combined arousal and valence ratings were selected for the present experiment. Overall agreement on the selected sample was 90.01% ± 8.50 for valence, 93.37% ± 8.29 for arousal and 84.94% ± 11.14 for the combination of both.

The 48 stimuli were grouped into 16 sets (4 for each emotional combination) of three related excerpts consisting of one target and two distractors used for immediate and delayed memory conditions. Length and style of each melody were matched to keep certain homogeneity between the target and the comparison excerpts. For this purpose, each set of three excerpts was composed by the same composer to increase homogeneity, except for one set from each emotional combination made with excerpts from different composers. List of symphonies is reported in Table 1 of Supplementary Material. Soloist passages were excluded to limit salient features that could play a role in encoding. All excerpts were normalized to maximal amplitude of 1.2 db. These stimuli were unknown to all participants as confirmed by post-test debriefing.

Procedure

The experimental task was run on a PC using Psychopy software. The experimental protocol included three phases: encoding, immediate recognition and delayed recognition. Prior to the beginning of the experiment, participants performed training during which they were shown an example of the test, ensuring they understood the task. During the encoding phase, subjects were presented with an intentional deep encoding task, being instructed to rate valence (positive/negative) and arousal (high/low) of 16 items and to retain them for a recognition test. The order of presentation of arousal and valence scales was counterbalanced across subjects. To reinforce encoding, subjects had an additional presentation of stimuli without the emotional rating task. Immediately after encoding, an old/new recognition test was presented. Sixteen targets were intermixed with 16 distractors in a randomized order. After each musical excerpt, participants had to decide whether or not the excerpt was already heard and to report if they were confident in their response (sure/unsure). After 24 h delay, participants were presented with the delayed recognition test including the 16 targets intermixed with 16 new distractors in a randomized order. Participants were again asked to perform recognition on the stimuli and to provide confidence ratings of their responses.

Data Analysis

Based on the accuracy of the response and the confidence ratings, receiver operating characteristic (ROC) curves were calculated for each arousal and valence combination. Three within-subjects factors were entered in a repeated measures analysis of variance (ANOVA): arousal (high/low), valence (positive/negative), time of testing (immediate/delayed), together with age (young/older) as between-subjects factor.

Results

Emotional Ratings

Preliminary analyses were carried out to test the effect of age on emotional judgment ratings for arousal and valence of musical excerpts (see **Table 1**). Ratings of each stimulus were transformed to z-scores and analyzed in two independent analyses of variance for arousal and valence respectively. An ANOVA with one within-subject factor (arousal) and one between-subject factor (age) was carried out on the arousal ratings obtained by young and older adults. The results revealed a main effect of arousal [$F_{(1,\ 58)} = 247.59\ p < 0.001$; $\eta^2 = 0.88$], the mean rating being higher for high than for low arousal changes as expected. There was no effect of age, nor any interaction between these factors.

Another ANOVA with one within subjects-factor (valence) and one between-subject factor (age) was carried out on the valence ratings by young and older adults. The results show a main effect of valence [$F_{(1,\ 58)} = 154.61$; $p < 0.001$; $\eta^2 = 0.73$], together with a valence by age interaction [$F_{(1,\ 58)} = 6.12$; $p < 0.001$; $\eta^2 = 0.22$]. Paired t-tests on the interaction pointed out that older adults rated positive excerpts as being less positive [$t_{(29)} = 3.74$; $p < 0.05$] and negative excerpts less negative [$t_{(29)} = -2.51$; $p < 0.05$] than young adults.

Recognition

The ANOVA with three within-subjects factors (Valence, Arousal, Time of testing) and one between-subjects factor (Age) was carried out on the areas under the ROC curves. This analysis revealed a main effect of Age [$F_{(1,\ 28)} = 26.71$; $p < 0.001$; $\eta^2 = 0.49$], the mean area under the curve being lower in old (mean ± SD = 0.74 ± 0.21) than in young adults (mean ± SD = 0.87 ± 0.13). However, the Age factor did not interact with any other factor. A main effect of Arousal was also obtained [$F_{(1,\ 28)} = 9.41$; $p < 0.01$; $\eta^2 = 0.25$], the mean area under the curve being higher for high (mean ± SD = 0.80 ± 0.18) than for low-arousing excerpts (mean ± SD = 0.73 ± 0.21) in the two groups. There was no main effect of Valence [$F_{(1,\ 28)} = 0.02$; $p > 0.05$] or of Time of testing [$F_{(1,\ 28)} = 0.35$; $p > 0.05$], but the analysis revealed an interaction between valence and time of testing [$F_{(1,\ 28)} = 11.51$; $p < 0.01$; $\eta^2 = 0.29$]. The analysis also showed a Time of testing by Arousal by Valence interaction [$F_{(1,\ 28)} = 5.85$; $p < 0.05$; $\eta^2 = 0.17$] such that Arousal and Valence differently interacted with scores obtained in immediate and in delayed recognition, as depicted in **Figure 1**. Thus, we conducted a new analysis including all participants separately for each time of testing to explore arousal by valence interactions.

Immediate recognition results revealed an interaction between Arousal and Valence [$F_{(1,\ 29)} = 5.67$; $p < 0.05$; $\eta^2 = 0.16$]. To reveal the sense of the interaction, simple effects of Valence on each Arousal level were explored using paired *t*-tests. We used Bonferroni correction of the statistical significance threshold, which was therefore set to $p < 0.0125$ (0.05/4) to correct for multiple comparisons. Whereas we found no difference between positive and negative excerpts for high arousing music, we showed that positive excerpts were better recognized than negative excerpts for low arousing music [$t_{(29)} = 2.77$; $p < 0.0125$]. Simple effects of Arousal on each Valence level did not yield any significant difference ($p > 0.0125$).

Delayed recognition results showed a main effect of Arousal [$F_{(1,\ 29)} = 13.92$; $p = 0.001$; $\eta^2 = 0.32$], with better recognition of high arousing (mean AUC = 0.83; *SD* = 0.17) than low arousing (mean AUC = 0.71; *SD* = 0.22) excerpts. There was also a main effect of Valence [$F_{(1,\ 29)} = 4.83$; $p < 0.05$; $\eta^2 = 0.14$] such that negative excerpts (mean AUC = 0.80; *SD* = 0.19) were better recognized than positive excerpts (mean AUC = 0.74; *SD* = 0.20). However, there was no interaction between these two factors ($p > 0.05$).

Discussion

In this study we have examined the effects of emotion in the recognition of symphonic musical excerpts for young and older adults. Arousal and valence of the musical excerpts were

TABLE 1 | Emotional judgement ratings *(z scores)*.

	Mean rating (mean ± SD)		
	Young	Aged	All
High arousal	0.64 ± 0.30	0.62 ± 0.43	0.63 ± 37
Low arousal	−0.64 ± 0.42	−0.62 ± 0.41	−0.63 ± 41
Positive valence	0.69 ± 0.32	0.35 ± 0.38	0.52 ± 0.39
Negative valence	−0.69 ± 0.49	−0.35 ± 0.65	−0.52 ± 0.59

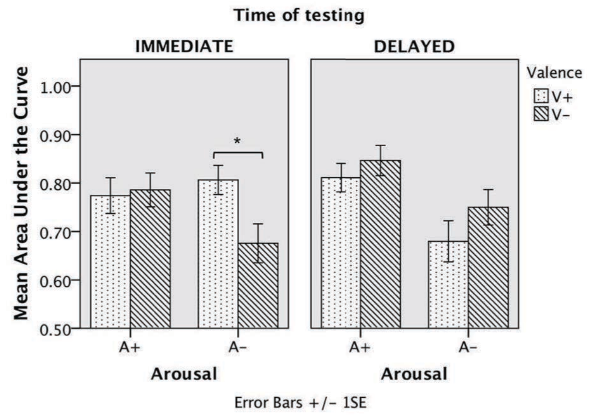

FIGURE 1 | Mean areas under the ROC curve for all participants from immediate and delayed recognition as a function of arousal and valence. Origin is set at chance level (0.50). The error bars correspond to the standard error of the mean. *$p < 0.0125$.

manipulated to address the impact of emotion on memory. Recognition memory tests were administered immediately after the study session, and also after a 24 h delay to measure effects that could be driven by consolidation. Although we confirmed an overall advantage in recognition performance for young over older adults, we were not able to demonstrate any further interaction with age for any of the emotional dimensions in immediate and delayed recognition.

This lack of interaction between age and emotional memory is in line with other studies using different kinds of stimuli such as pictures (Kensinger et al., 2002, 2007; Denburg et al., 2003; Kensinger and Schacter, 2008; Waring and Kensinger, 2009), words (Kensinger et al., 2002; Grühn et al., 2005; Mickley Steinmetz et al., 2010b), scenes (Otani et al., 2007; Murty et al., 2009), and music (Vieillard and Gilet, 2013), which have also failed to show an effect of aging on emotional memory despite the positive bias described in the literature. Mather (2006) suggests that the positive bias effect shown in aging may need strategic and goal-oriented processing of the emotional stimuli to affect memory (see also Mather and Knight, 2005), thus being susceptible to elaboration on the stimuli processing and to participant's motivation. However, as suggested by Dellacherie et al. (2011), real musical performances may intensify motivational significance of the stimuli more than prototypical clips (Vieillard et al., 2008), and thus our stimuli should have successfully engaged participants on the encoding task. Nevertheless, it is possible, that such successful engagement on the task may have minimized potential differences between young and older adults. Importantly, to enhance homogeneity between the different valence/arousal combinations, we limited the music genre to classical music, which might be less emotionally evocative to some participants than other more popular music genres. Thus, further studies sampling a wider range of musical genres are needed to replicate the present emotional memory findings.

Since no interaction with age was found, subsequent assessment of emotional memory was performed for all participants without an age group distinction. We found a double interaction between valence, arousal and time of testing, indicating that arousal and valence had different memory effects at each testing delay. This result supports the idea that early effects of emotion on memory may vary with delay, suggesting that emotions may influence memory consolidation (Talmi, 2013; Leal and Yassa, 2014).

The immediate recognition analysis revealed an interaction between arousal and valence. Whereas valence does not seem to affect recognition of high arousing excerpts, it modifies recognition of low arousing stimuli such that positive excerpts were better recognized than negative excerpts. This result highlights the relevance of valence for low arousing excerpts in immediate testing, in line with Streubel and Kunzmann (2011), who suggest that the positivity bias on emotional reaction may be restricted to low arousing stimuli. Moreover, our finding is in agreement with Kensinger (2008), who also found an interaction whereby more positive non-arousing words were remembered relative to negative non-arousing words for older adults, but no valence effect was found for high arousing words. Nevertheless, an age difference was found in that study, with younger adults having better memory for negative than positive non-arousing words, therefore presenting an effect of valence on low-arousing words in the opposite direction to the older group. Our results also contrast with Leal and Yassa (2014), who found a benefit for emotional valenced pictures over neutral pictures in older adults and the reverse pattern in younger adults. It may be possible that the difference between these previous studies and the present study may be material specific. Most importantly, no particular advantage was found for high arousing negative valence excerpts. As we have previously discussed, few studies have suggested a benefit for "fear" music (Aubé et al., 2013; Vieillard and Gilet, 2013), but such memory effect might have been biased by a difference in the discriminability between the "fear" music and the other emotional music (Samson et al., 2009). Conversely, our results suggest that memory for high arousing excerpts may not differ for negative and positive valence, with only worst memory for negative low arousing excerpts as compared to positive low arousing excerpts.

After a 24 h delay, all participants had better memory for high than low arousing excerpts. The lack of difference between young and older adults on such arousal effect on memory has also been reported for words (Kensinger, 2008) and visual scenes (Otani et al., 2007). The benefit for high arousing music as compared to low arousing music on delayed recognition is in line with Eschrich et al. (2005). This finding highlights the stronger effects of arousal after a delay, supporting the influence of arousal in consolidation. High arousing music remained well remembered also in older adults, in accordance with results from Waring and Kensinger (2009) using emotional images (for opposing results see Leal and Yassa, 2014).

Furthermore, after a 24 h delay, all participants have better memory for negative than positive excerpts. This is in agreement with studies in other domains that have shown a memory advantage for negative over positive stimuli (Waring and Kensinger, 2009). Conversely, our findings are at odds with Eschrich et al. (2008) who found a benefit for very positive musical excerpts over less positive musical excerpts on recognition following a 24 h delay. However, a recent study using similar music stimuli to that of Eschrich et al. (2008) but with a shorter presentation (10 s), has failed to replicate this valence effect on recognition (Altenmüller et al., 2014). It is possible that the advantage for very positive over less positive excerpts may be tied to longer presentations (20–30 s). We cannot exclude, nonetheless, that higher degree of positivity within the positive excerpts, (which is not measured in the present study), may enhance recognition even when negative excerpts could be better recognized. In sum, the valence effect found after 24 h delay, and not during immediate recognition, argues in favor of an enhancement effect of consolidation not only for high arousing stimuli but also for negatively valenced stimuli in line with Waring and Kensinger (2009). Nevertheless, the greater effect size of arousal supports the predominant influence of this dimension on consolidation reported in the literature (for a review see McGaugh, 2000, 2004). Of note, besides the emotional memory immediate and delayed effects, overall memory performance did not seem to decay after 24 h delay, supporting the durability of memory for emotional stimuli. Additionally, despite the interaction between time of test, arousal and valence found in the initial analysis, the presence of a main effect of arousal in that analysis further suggests the stronger impact of this dimension on memory performance overall.

The ability to evoke comparable ratings of high/low arousing and positive/negative valence of the musical excerpts represent a strength of this study. The presence of interactions between arousal and valence on immediate recognition further highlights the pertinence of manipulating emotional dimensions on experiments addressing emotion effects on memory, as it has been already suggested for words (Citron et al., 2014). The analysis of participant's judgment ratings of the music excerpts validated that the emotional characteristics of stimuli regarding arousal and valence were well distinguished. The analysis of the arousal emotional judgment confirmed that arousal ratings correctly reflected arousal differences in the stimuli. Although it has been reported that age can affect the arousal rating of music (Vieillard et al., 2012), no different ratings for arousal were found between age groups for the present stimuli set. Conversely, the analysis on valence ratings showed an interaction between valence and aging, suggesting that older adults rated positive excerpts less positive and negative excerpts less negative than young adults. Differences between older and younger adult groups in the valence of emotional judgments have been already reported for music (Lima and Castro, 2011), indicating more positive ratings for negative stimuli, which can partially account for the present interaction found between ratings of valence and age. Although the valence rating analysis suggests that older adults manipulated a smaller valence range than the young group to judge valence, still positive excerpts were rated more positive than negative excerpts within this group, indicating that they could distinguish valence well within the musical stimuli used in the present study. Most importantly, the effect of valence on memory did not differ between young and older adults. Furthermore, ratings of arousal and valence were clearly dissociated, also for older adults, suggesting there to be independent emotional identification of these two dimensions for the presented music stimuli.

It is worth mentioning that some authors have argued that music evoking negative emotions is very rare (Baumgartner et al., 2006a,b). However, as illustrated by film music, music has succeeded in representing and evoking emotions like sadness, rage, or fear, which lay within the negative valence spectrum (Boltz et al., 1991; Cohen, 2001; Boltz, 2004; Juslin and Laukka, 2004; Mitterschiffthaler et al., 2007; Juslin and Västfjäll, 2008; for a review on music emotions see Kawakami et al., 2014). To this end, the present study contributes toward the differentiation of arousal and valence dimensions on music in an effort to understand their effects on memory. The stimuli used in this study were able to express the intended emotions resulting from the manipulation of arousal and valence dimensions as attested by emotional ratings.

In the present study, the participants were explicitly instructed to remember the musical excerpts while rating emotional valence and arousal of each excerpt during the encoding phase. It is possible that intentional encoding, together with the emotional rating task, may have elicited deeper encoding for all items (Craik and Lockhart, 1972), posing one important limitation to the present study. It could be argued that emotional effects on memory are more prominent for shallow encoding tasks than deep encoding tasks (Ritchey et al., 2011). In contrast, other studies (Hess et al., 2013; Broderick et al., 2014) did not found differences in emotional memory when comparing intentional to incidental encoding instructions. Nevertheless, we cannot rule out that a shallow encoding task may have resulted in greater emotional impact than our intentional encoding/emotional rating task, or even had emphasized differences between age groups.

Another caveat of this study is that although both groups had comparable educational levels, musical expertise, and anxiety levels, our sample was small, with 15 participants in each group, and age was more variable within the old group than the young group. To enhance the sensitivity to age differences, we selected only participants younger than 25 years old and older than 60 years old. A larger sample of participants that may gradually cover all ages may support the generalization of the present findings. Furthermore, studies particularly looking at other psychological factors within a broader aging population may contribute to a better understanding of which conditions could affect emotional memory in aging.

The present findings contribute to the investigation of arousal and valence effects of music on memory in aging. This has important clinical implications, suggesting that the ability to detect emotional valence and arousal in music and recognize emotional music does not seem to be affected by aging, which might explain the efficacy of interventions such as the reminiscence therapy cued by music (Woods et al., 2005; Cotelli et al., 2012). The increasing demands for intervention programs to promote healthy aging and the preservation of cognitive functions, such as memory, can benefit from scientific evidence as such reported here (Reijnders et al., 2013). Based on its emotional power, music has been increasingly used in therapeutic settings with dementia and aging populations (Clément et al., 2012; Narme et al., 2014; Särkämö et al., 2014; for a review see McDermott et al., 2012; Raglio et al., 2012; Ueda et al., 2013). Understanding how emotional characteristics of music may contribute to memory can help to develop interventions and activities that promote healthy aging. In light of these findings, future studies with more detailed sampling of an aging population, eventually including a range from healthy to different degrees of cognitive impairment, and a variety of music genre, may further contribute to explore the potential benefits of music interventions in aging.

Conclusion

In sum, although older adults performed generally worse than younger adults on music recognition, we were not able to demonstrate age differences on emotional memory for music. The musical excerpts selected for this study allowed the assessment of arousal and valence effects of emotion on recognition, providing equal distinctiveness between the four resulting emotional combinations of arousal and valence. Overall, we present novel evidence on emotional memory for music in young and older adults, immediately and after 24 h delay, by manipulating both arousal and valence dimensions. Immediate recognition results showed that low-arousing but not high-arousing music could be modulated by valence. Both groups showed a benefit for positive as compared to negative music when arousal was low. However, recognition after a 24 h delay, showed a benefit for high over low arousing stimuli and an effect of valence whereby negative excerpts were better recognized than positive excerpts. These findings highlight the impact of emotion on consolidation in memory. Future studies including larger samples of participants covering a broader age range and isolating factors like depth of encoding are highly encouraged to further understand emotional memory for music and how it could be affected by aging.

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Supplementary Material

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fnagi.2015.00023/abstract

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Music in the rehabilitation of patients with memory and learning deficits. International workshop - Lille 2013.

See : https://prezi.com/gcssjfjzu3m5/music-in-rehabilitation-of-memory-and-learning-deficits

Program

Music in the rehabilitation of patients with memory and learning deficits

Lille 17-18 January 2013

Université de Lille Nord-de-France

INSTITUTE FOR MUSIC IN
HUMAN AND SOCIAL
DEVELOPMENT
[IMHSD]

As reflected in the last Neurosciences and Music Conference (2011), memory and learning are becoming main areas of focus in music neuroscience research. More specifically, the potential of music as a rehabilitation tool in learning and memory disorders warrants further empirical research and stronger links with practice that can move research findings into the clinic. The aim of this workshop is to bring together researchers with expertise in music and the brain, and individuals who use music in practice with populations with learning and/or memory deficits. The state-of-the-art of music in the rehabilitation and well-being of patients with learning and memory deficits will be discussed - we will review the applicability of the current findings and future trends in research. A series of short presentations will precede open panel discussions to provide a space for debate and stimulate future collaborations.

This workshop is organized in the frame of the third work package of the project Europe BRAin and MUSic (grant agreement 238157).

Thursday 17th of January

13h00 Registration

13h10 Welcome

Pathways for the Effects of Music

13h20	Can music increase spatial awareness in visual neglect?	**Lauren Stewart**
13h40	Implicit learning in patient populations	**Tatiana Selchenkova**
14h00	Functional brain plasticity induced by musical practice – training effects versus individual predisposition	**Sibylle Herholz**
14h20	How can musical practice influence cognitive and emotion-related abilities?	**César Lima**
14h40	**DISCUSSION** Chairs:	**Emmanuel Bigand & Barbara Tillmann**

15h20 Coffee pause

Music & Memory

15h40	Memory for Familiar and Unfamiliar Music in Alzheimer's Disease	**Andrea Halpern**
16h00	Music-evoked autobiographical memory in Alzheimer's Disease	**Mohamad El Haj**
16h20	Auditory Binding : imaged encoding of songs	**Irene Alonso**
16h40	Musical Spam task	**Sylvain Clement**
17h00	**DISCUSSION** Chair: **Andre Halpern**	

20h00 Dinner at "Philip"

(19, rue de Gand 59000 VIEUX LILLE)

Friday 18th of January

Music Interventions

9h00	Musical attention and memory training as a primer for learning and engagement in songwriting for rehabilitation	**Jonathan Pool**
9h00	Musical interventions in patients with moderate to severe dementia	**Pauline Narme**
9h00	Music in everyday life; Real world examples of individuals living with moderate dementia	**Liz Dennis**

15h20 Coffee pause

10h20	Creative music projects with the over 60s	**Lucy Forde**
10h20	**DISCUSSION** Chairs:	**Hervé Platel & Séverine Samson**

Music Technology

11h40	Demo	**Marc Leman**

12h00 Lunch

Music & Language Deficits

13h20	Musical rhythms to enhance speech processing: speech re/habilitation contexts	**Nia Cason**
13h40	The role of music in word re-learning in aphasia: What's the role of the therapist?	**Laura Verga**
14h00	Music in dyslexia	**Clement Planchou**
14h20	**DISCUSSION** Chairs:	**Sonja Kotz & Katie Overy**

15h00 Coffee pause

Future Trends and Applicability of Research

15h20	Near-Infrared Spectroscopy: an emerging tool for research in cognitive psychology	**Laura Ferreri**
15h40	Imagery as a rehabilitation tool	**Rebecca Schaefer**
16h00	**DISCUSSION** Chairs :	**I. Alonso, K. Overy & S. Samson**

16h30 Farewell snacks

Amphi G, Université Lille 3
(Métro : Pont de Bois)

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