The contribution of the hippocampus to language processing

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Abstract

Humans display distinct unlimited capacity to produce expressions in language and use them flexibly in language processing.This characteristic of human language allows speakers to use novel, flexible, and complex structures during communication. Neurobiologically, however, it is not fully understood how the rapid process of language production and language comprehension occurs, including word generation, interpretations and common representations that facilitate the process of real-time language processing. The classical theories and approaches have limited the language network to perisylvian cortical regions, namely the Broca's and Wernicke's areas. This thesis proposes that the language network goes beyond the cortical regions indicated by traditional views. In doing so, this thesis puts forward a hypothesis that subcortical structures are not only fundamental to memory but also to language, in which online language processing receives a major contribution from the hippocampal declarative memory, which allows speakers and listeners to use language flexibly. The mechanism of such a contribution by the hippocampal declarative memory system during online language processing is via relational binding in which hippocampal declarative memory rapidly retrieves a network of relative, stored information to serve in the particular context.

To support the hypothesis of hippocampal implications in language processing, several pathologies that affect the hippocampus have been reviewed, including Alzheimer's disease, Down syndrome, Williams' syndrome, schizophrenia, depression and bipolar disorder. The review evaluated hippocampal neurobiological alterations in each pathology, and determined cognitive and language profiles. Findings from previous pathologies indicate that the hippocampus affects language at two levels. First, in the general delay in language acquisition and other cognitive aspects, and second, in the disturbed use of language during online communication; short lag interaction is seen to occur when the hippocampal formation is lesioned. It appears that hippocampal lesions suppress the flexible use of stored information within certain contexts in communication, as it does in flexible navigation in animal models. This thesis concludes that the hippocampus is a multi-cognitive operator that is implicated in several cognitive areas including the flexible use of language during real-time processing, and therefore it should be taken into account in the language network in the human brain.

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Chapter 1

Introduction

This thesis aims to extend the classical map of the "language network" in the human brain into a wider network in which the hippocampus is accounted. The thesis discusses multiple issues in which hippocampal declarative memory plays a crucial role in online language processing. Unlike other species in the animal kingdom, humans are excellent at communication and social interaction due to high-level cognitive functions (Hauser et al., 2002). I suggest that the traditional view of the brain is no longer sufficient for an understanding of the language network in the human brain, and the time is ripe for a major reconstruction of the neurobiological map of human language, exploiting advanced techniques in cognitive neuroscience to explore the contributions made by subcortical structures in the brain. Nevertheless, my proposal does not discard what are labelled "language regions" but considers them as a single node in a larger network.

1.1 Classical neuropsychology of language

The field of neuropsychology has been the main source for framing the language network in the brain. Determining which region of human brain is responsible for language processing was begun by pioneers physucuan Paul Broca Broca (1861), who based his observations of the left prefrontal cortex of two patients who suffered injury to the posterior frontal gyrus, in the areas named 44 and 45 by German neurologist Korbinnian Brodmann. As a result of their injuries, the patients displayed major difficulties in vocalization, in a condition now known as Broca's aphasia. Neural connectivity within Broca's area varies: area 44 receives inputs from motor, somatosensory, and inferior parietal regions, and area 45 corresponds to the prefrontal cortex, the superior temporal gyrus, and the superior temporal sulcus (Deacon, 1992; Petrides and Pandya, 2002). Neuroimaging data indicate inferior frontal gyrus activation during language comprehension tasks; likewise, it performs a syntactic unification function (Hagoort, 2005).

In contrast to the language production function of Broca's area, Carl Wernicke suggests that Brodmann area 22 in the posterior region of the superior gyrus is implicated in language comprehension, and is now known as Wernicke's area (Figure 1.1). In patients with a damaged posterior superior gyrus, the ability to grasp meaning of sentences is impaired, however, the ability to produce connected speech is not very affected. The sentences these patients produce are often meaningless. This condition is known as fluent aphasia (Prather et al., 1997).

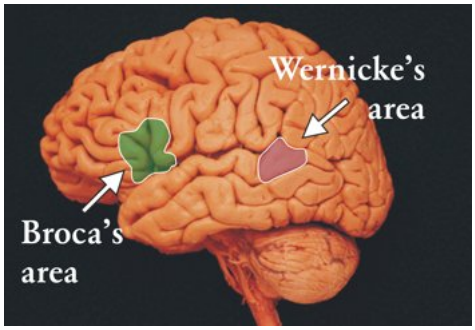


Figure 1.1: Brain image of Broca's and Wernicke's areas in the left hemisphere of the human brain.

1.2 Pathways for language

Due to the modularity of classic theory, which distributes language aspects among the frontal and temporal cortex (Broca's and Wernicke's area), advanced brain imaging and current biolinguistic research tend to highlight anatomical findings of functional connectivity between Broca's and Wernicke's areas that stand out in the evolution of human language. Diffusion tensor imaging (DTI) allows scholars to trace connection pathways of the white matter in a living human brain. An important neurological feature of our faculty of language is the arcuate fasciculus (AF), which is a bidirectional axon bundle connecting the temporal lobe to the frontal lobe via the parietal cortex (Figure. 1.2). Connectivity between the temporal and frontal lobes differs substantially between humans and other species. The AF contains short and long fibers across temporal, frontal, and parietal lobes in both hemispheres (Catani and De Schotten, 2008), and the AF is or significantly smaller in other primates. Rhesus macaque monkeys display activation in the superior-temporal gyrus during voice recognition of "conspecific" individuals, which meshes well with fMRI observations of the human auditory cortex (Petkov et al., 2008). In our closest relatives,

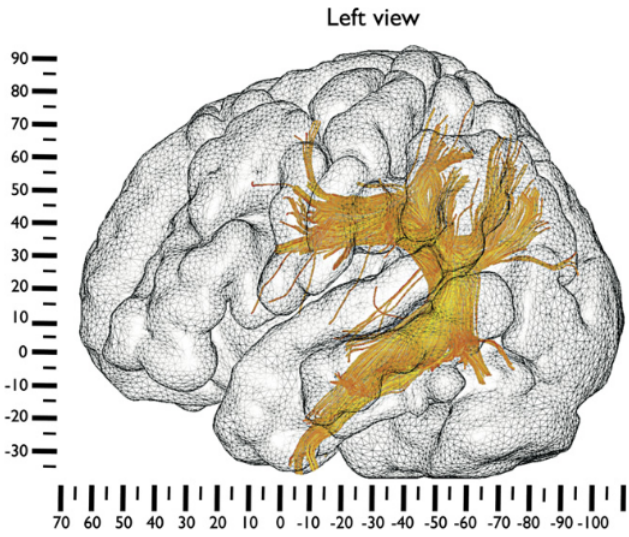


Figure 1.2: Illustration of arcuate fasciulus connecting frontal and parietal-temporal cortex in the left hemispheres of human brain, including Broca's area and Wernicke's area. Adapted from (Catani and De Schotten, 2008).

chimpanzees and macaques, humans show stronger frontal-medial temporal gyrus connections in both dorsal and ventral forms of AF. In addition to our well-developed prefrontal cortex, Rilling et al. (2008). Research results suggest that modified pathways in the human brain enable us to execute complex syntactic structures and high-level cognitive performance (Figure 1.3). Evidence from incidents of language impairment indicates that lesions in the AF leads to conduction aphasia. Conduction aphasic patients maintain intact language comprehension and language production, however, they experience speech repetition deficits in especially complex syntactic phrases, and naming difficulties (Damasio and Damasio, 1980). It is often reported that conduction aphasia affects adjacent AF areas and axon bundles that may contribute to the temporal-frontal circuit (Bernal and Ardila, 2009). Nevertheless, conduction aphasia warrants further investigation.

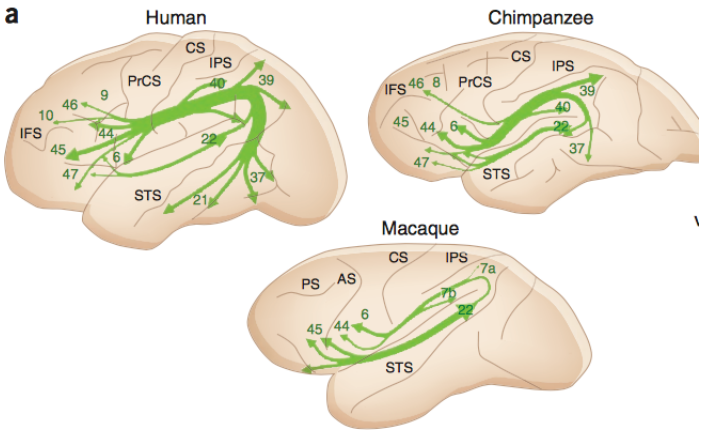


Figure 1.3: Humans evolved a solid form of arcuate fasciulus compared to chimpanzees and macaque monkeys (Ghazanfar, 2008).

As current investigation of the AF continues, scholars have found that the AF is enhanced by other forms that connect the Broca's and Wernicke's areas. Two dual pathways are believed to play a significant role in language processing: the dorsal pathway from Wernicke's area to Broca's area via the AF, the superior longitudinal fasciculus and connectivity to Brodmann 40 to the lateral superior temporal gyrus and lateral medial temporal gyrus. The ventral pathway links Wernicke's area and Broca's area through the uncinate fasciculus, the extreme capsule and the medial superior temporal gyrus (Parker et al., 2005). Through high-resolution brain imaging, Catani et al. (2005) were able to detect dual dorsal pathways, alongside the known AF direct projection between Broca's and Wernicke's area, with an indirect pathway parallel to the AF pathway and connecting Brocas area to the inferior parietal lobe followed by projection to Wernicke's area (Figure 1.4). Cognitively, dorsal and ventral pathways in humans are associated to "what" and "where" streams respectively (Hickok and Poeppel, 2000). The neuroanatomical development of dorsal and ventral pathways is robust

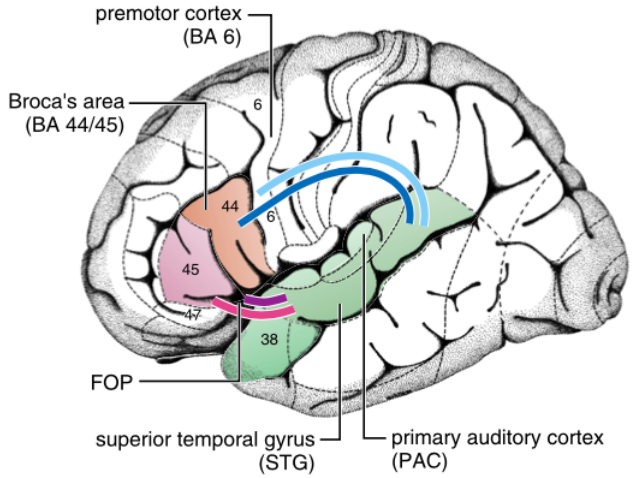


Figure 1.4: Projection of dorsal pathways (blue) and ventral pathways(red). Adapted from (Friederici, 2011).

evidence for its substantial implication in language processing. To some extent the dissociation of dorsal pathways divides the labour between the two pathways, and findings suggest that the dorsal pathway vis superior longitudinal fasciculus to boosts our competence in complex linguistic processes (Parker et al., 2005). Brauer et al. (2013) observed dorsal and ventral pathway maturation in newborns, children and adults. Dual dorsal pathways vary in maturation phases during infancy. The newborn dorsal connection (D1) to the premotor cortex is present in early life to support sensory-to-motor mapping (Saur et al., 2008). However, the other dorsal pathway (D2) connecting to Broca's area is not present in newborns. Unlike that group, seven-year-old children display more maturation of dorsal and ventral pathways, which is relatively similar to adults. On the other hand, the ventral pathways connecting Broca's area to the temporal cortex rapidly develop in newborn infants. Even though DS initial development is unknown, Brauer et al. (2013) argue that late maturation of the D2 gives rise to higher lan-

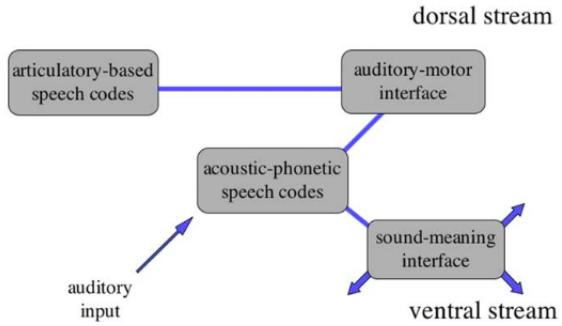


Figure 1.5: Schema of linguistic functions of ventral and dorsal streams. (Hickok and Poeppel, 2000).

guage function in children and adults.

To demonstrate the linguistic functions of a new neurobiological model of language, Hickok and Poeppel (2004) proposed that ventral pathways primarily translate sound into meaning and dorsal pathways are implicated in transforming sound into representative articulation. To assure previous hypotheses of the distinct linguistic functions of each pathway, two experiments of real and pseudo words using loud repetition and a listening task of meaningful and meaningless phrases were observed via fMRI. Findings reinforced prior proposals of the two parallel pathways within the dorsal and ventral streams. Word repetition seemed joined by activation in the superior temporal and premotor cortex, while the middle and inferior temporal regions and ventrolateral prefrontal cortex were activated during listening and comprehension tasks (Brauer et al., 2013).

In sum, the biolinguistic field witnessed mass developments in empirical studies due to state-of-the-art techniques and consequent rapid growth in biology and neurophysiology. The delineation of principle issues in the neurobiology of language has thus far been fruitful. Nevertheless, there is a

general tendency to rely on nineteenth-century determinations in the localization of language within the brain (Dronkers, 2000). The current state of the research limits the wide language network to Broca's for production and Wernicke's for comprehension with their fiber connection (AF), implying these are the only neurological components of language network.

One fact that the classical model omits is that language is not a solitary or single event, rather it receives numerous contributions from other cognitive domains. For instance, current literature seems to hold memory as isolated from the language network, which logically seems to make no sense. Various attempts towards a novel neurobiological framework for language have failed to extend the network beyond the traditional vision, even in hypotheses by Hickok and Poeppel (2000). The object of which, however, does not imply invalidity of classical views but, rather, displays the necessity to take advantage of cutting-edge technology to explore other brain regions that have not been yet investigated in relation to language processing.

Poeppel and Hickok (2004), state three issues about the Broca and Wernicke's model, which are worth mentioning. First, language pathology and aphasia have long implicated the Broca and Wernicke's areas as playing a central role in language. However, some types of aphasia may occur in other brain regions and lead to language deficits as well. For instance, anomic aphasic patients experience failures in word retrieval, and findings have localized the relevant lesion area in the left inferior parietal lobe (Fridriksson et al., 2010). Likewise, instances of other diseases and syndromes discussed in the forthcoming chapters also indicate language deficits associated with brain lesions in the cortex and subcortex. Second, the Broca and Wernicke's

areas model is relatively vague in their areas' functional attribution, referring to broad concepts of production and comprehension. This "impoverished" model neglects detailed linguistic aspects, such as syntax, semantics, and phonology. But in fact, each of previous aspects is composed of subcomponents that cannot be accommodated in one single area in the brain. Third, anatomical issues are present in language pathology and aphasia, and it is unlikely that one specific region can be affected to the exclusion of adjacent areas. Broca's aphasia can be caused by lesions in the regions neighbouring Broca's area (Mohr et al., 1978). In a reported case of a resected Broca's area, the patient continued to be able to produce normal speech (Plaza et al., 2009). Further, conduction aphasia is not limited to the AF, as has been indicated by the observation of a patient which suggested cortical dysfunction (Anderson et al., 1999).

Previous evidence sufficiently demonstrates the limitations of the traditional view of limiting language to the Broca and Wernicke's areas and the AF connecting the two regions. Anatomically, the language network should be extended to include other regions that have been overlooked by the current inadequate map of language processing.

1.3 Anatomy of the hippocampal formation

The hippocampus is so named due to its resemblance in shape to the seahorse as indicated in the Greek language. The hippocampus is one of the major components of the subcortex located under the cerebral cortex (Figure 1.6), and is preserved across the vertebrates. The case of Henry Molaison (H.M.) is the most investigated case in the neurobiology of human brain.

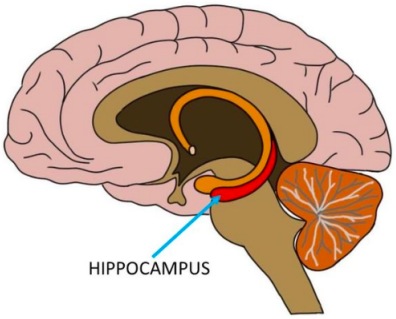


Figure 1.6: The hippocampus is one of the most explored subcortical structures.

H.M. suffered intractable epileptic seizures that led to a resection in 1953 of his medial temporal-lobe, including two-thirds of the hippocampus (Scoville and Milner, 1957). Cognitively, findings from H.M.'s case have yielded insights and improved our understanding of human memory and central hippocampal role. H.M. was incapable of forming novel memories, or retrieving memories recent to the resection, which indicated the hippocsmpus' capacity to consolidate but not to store information (Scoville and Milner, 1957). Likewise, he exhibited severe impairment in navigation (for an extended review of the case, see (Corkin, 2002)). Nevertheless, the H.M. case poses a challenge to identify the precise role of the hippocampus due to the prevalence of lesions to the areas adjacent to the hippocampus, including the amygdala and the parahippocampal gyrus. Comparative biological evidence from monkeys has shown mild memory loss due to lesion in the hippocampus, whereas more severe memory impairment has been observed when the hippocampal complex, including the entorhinal cortex and parahippocampal gyrus, was damaged (Zola-Morgan et al., 1994).

Anatomically, the hippocampus consists of the dentate gyrus, cornu ammonis (CA1, 2 and 3), and the subiculum. The neuroanatomy of the hip-

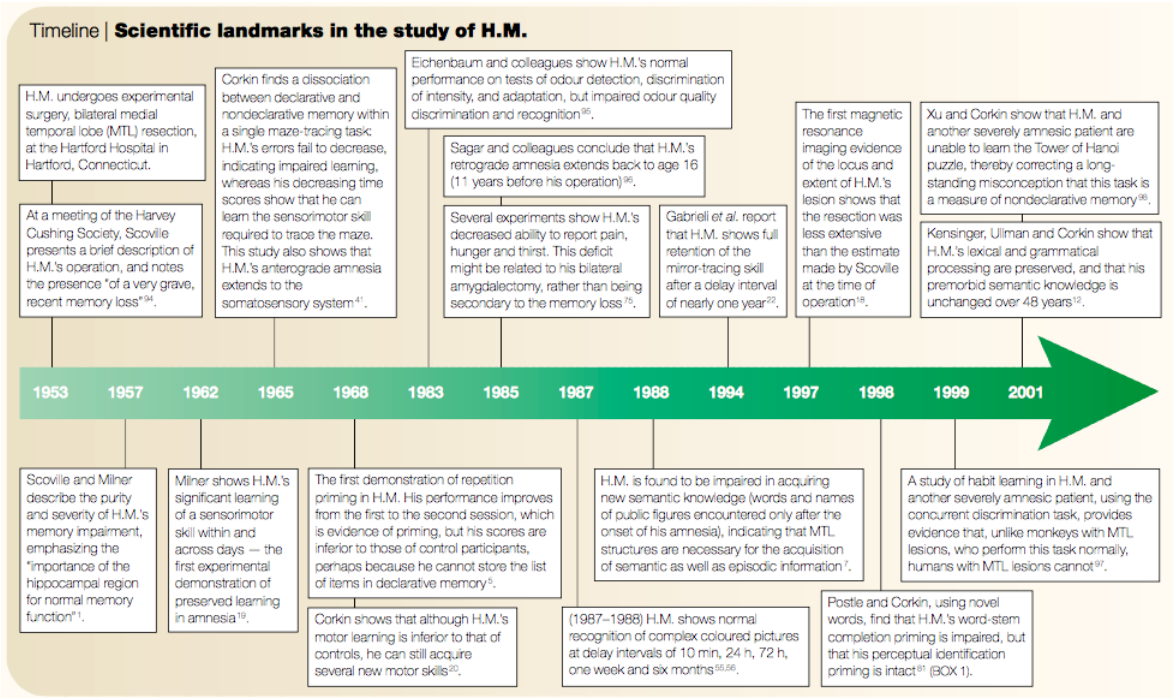


Figure 1.7: Timeline of scientific landmarks of H.M. case after the patient's bilateral hippocampal resection. Reused with permission from (Corkin, 2002).

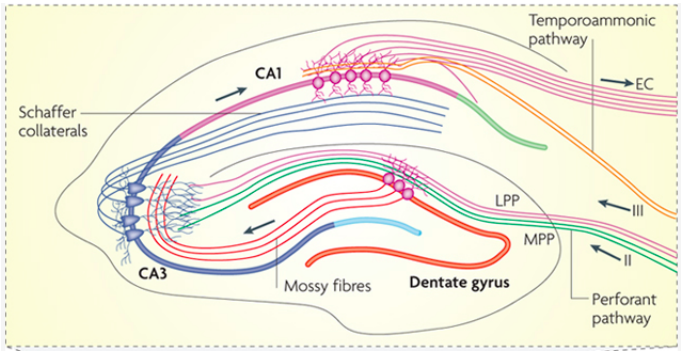


Figure 1.8: Unidirectional hippocampal circuit, where the EC initiates projection and receives the last signal in the circle (Deng et al., 2010).

pocampus is distinct from the cortex. The hippocampus receives multimodal sensory inputs from various neocortical regions, and the connectivity pattern of hippocampal subdivisions is unidirectional. The entorhinal cortex (EC) is the initial sender of signals in the hippocampal circuit; the neocortex mainly projects to the EC. EC cells then activate axons that project to the dentate gyrus. Although the EC projects to the CA3, it is the EC-DG projection that is the major pathway of the hippocampal input, which is known as the perforant pathway. In turn, the DG granule cells send signals to the CA3 via mossy fibres, which activate the pyramidal cells of CA3 to provide main input to CA1. The CA1 then porjects to the subiculum, and both accomplish the trisynaptic circle to the EC (Figure 1.8) (David and Pierre, 2009; Klausberger and Somogyi, 2008; Tonegawa and McHugh, 2008; Moser, 2011; Insausti et al., 2017).

Despite the importance of the EC as a hippocampal resource of inputs, the question that arises here is: from where does the EC receive inputs?. Indeed, the answer to this question is as yet unsolved, however, two cortical regions are of significant importance to our topic. First, the superior temporal gyrus

is implicated in multisensory processing and the interpretation of speech and vocal input (Hickok and Poeppel, 2007; Senkowski et al., 2008). And second, the superior temporal sulcus is a multisensory hub that integrates inputs from the visual and auditory cortex (Baylis et al., 1987). Evidence indicates a direct connection between the superior temporal gyrus to the EC in studies of monkeys (Amaral et al., 1983; Insausti and Amaral, 2008).

In contrast, data of hippocampal projection to the superior temporal gyrus is scarce. Another region, related to the thesis is the PFC projection to the hippocampus. MPC is an important bidirectional projection to the EC with an intensive projection to the anterior more than to the posterior EC (Morecraft et al., 2012; Insausti and Amaral, 2008). However, the most intensive hippocampal projection is CA1 to Brodmann areas 25 and 32 (Insausti and Munoz, 2001). Likewise, the orbitofrontal cortex, which receives sensory inputs from various regions, reciprocally projects to the EC and the parahippocampal gyrus (Cavada et al., 2000; Insausti and Amaral, 2008). In sum, unlike intrinsic hippocampal connectivity, which has been well demonstrated to be linked to memory and navigation tasks, extrinsic connectivity of the hippocampus should display the importance and complexity of the hippocampal declarative memory and how such connections facilitate episodic memory and contextual information processing.

In his studies of relevant subcortical participation in language and cognition, Ullman (2001a) puts forth a declarative-procedural (DP) model of language processing. The model posits that language relies on two subsets of long-term memory: declarative and procedural memory. Both forms of memory have been documented at cognitive, and biological levels, which led

Ullman to apply the model to first and second language processing. Briefly, the declarative memory system is responsible for learning, representation, general knowledge, memory of facts, and personal experience (Squire, 2004). The hippocampus is a major hub of memory formation, learning, and consolidation. On the other hand, procedural memory is responsible for unconscious learning, motor and cognitive skills, and execution of the consequences of motor learning. The basal ganglia underlies procedural processes in concert with the frontal cortex (Eichenbaum and Cohen, 2004). Ullman (2001b) proposes that different aspects of language are associated with different neurocognitive systems. Based on the DP model, a mental lexicon is stored in the declarative memory of the hippocampus and mental grammar is computed in the procedural memory of the basal ganglia and frontal lobe. In other words, declarative memory maintains subcomponents of a mental lexicon, such as words and their meaning, irregular morphology, and irregular forms of verbs, while procedural memory applies rule-governed sequences of structures, such as regular verb forms of past, present, and future tenses.

Although, these memory systems are distinct, both cooperate and compete in learning processes (Poldrack and Packard, 2003; Schreiweis et al., 2014). In animal studies, hippocampal lesions enhance procedural learning in the basal ganglia (Schroeder et al., 2002). A large body of evidence supports the DP model of language processing in humans. fMRIs reveal activation in the left hippocampal and parahippocampal gyri during semantic tasks (Newman et al., 2001). Specific language impairment provides solid evidence of grammatical impairment and dysfunction in procedural memory underpinnings (Ullman and Gopnik, 1999). Aphasia is the prime source of evidence in the Broca-Wernicke model, and non-fluent aphasia findings often

indicate a damaged broca's area, and basal ganglia lesion (Damasio, 1992; Dronkers et al., 2000). Neurodegenerative diseases, such as Alzheimer's disease, target the hippocampus in early stages of the disease; in contrast, the basal ganglia and Broca's area often remain healthy. Generally, AD patients are incapable of acquiring new words or retrieving stored lexical items (Ullman, 2004).

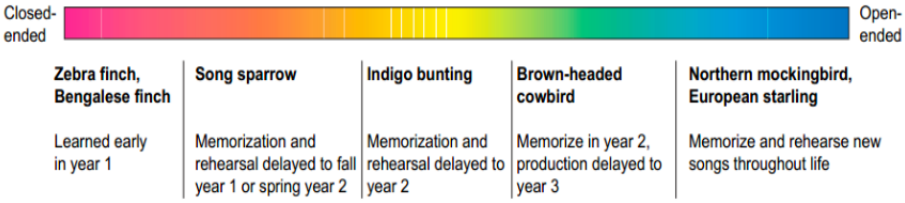
Ullman's model is one of a few proposals that reinforce the importance of the medial temporal lobe (MTL) in the brain's language network. Cognitive and clinical evidence is growing. What is needed is further examinations of patterns of non-linguistic aspects in the declarative and procedural systems in order to develop a DP model in the subcortex.

From a biological perspective, a comparison between hippocampal volume and song learning in vocal-learning birds can be made. Interestingly, (Alamri and Qing Zhang, 2016) found a positive association between the volume of the hippocampus and song-learning plasticity (Table 1.1). The great diversity of song-learning capacity and subcortical volumetric variations among songbirds could advance our understanding of the neurobiological the underpinnings of vocal learning and language.

Open-ended and close-ended vocal learning birds

- Open-ended learning: song plasticity as adults.
- Close-ended learning: no song changes after sensitive period.

A



B

species		Log (hippocampus)
Lonchura striata	Bengalese finch	0.824
Taeniopygia guttata	zebra finch	0.700
Troglodytes groglodytes	winter wren	1.093
Turdus merula	blackbird (European)	1.593
Sturnus vulgaris	starling	1.459

Table 1.1: A: Continuum between close-ended and open-ended song learning. Adapted from(Brenowitz and Beecher, 2005). B: Hippocampal volume (the volumes are in cubic millimetres and have been log transformed), (Devoogd et al., 1993).

1.4 The hippocampus and cognitive flexibility in animals

Cognitive flexibility refers to the brain's readiness to switch and adapt thinking to the demands of external stimuli (Scott, 1962). Noninvasive fMRI findings of the neural network during cognitive flexibility tasks reveals activation in the basal ganglia, anterior cingulate cortex, prefrontal cortex, and posterior parietal cortex (Leber et al., 2008). As Duff and Brown-Schmidt (2012) propose, I suggest that creative structures of human language during real-time communication and social interaction require a higher order of flexibility and coordination. Equally important is flexibility in other cognitive domains such as navigation and decision-making. Hence, I suggest that animal models of flexibility are of great importance in understanding

mechanism and the contribution of subcortical regions.

Experimental cognitive studies of spatial navigation suggest a major contribution credited to flexibility. The nature of navigation is that it must be adaptable to environmental alterations, or have what is known as spatial flexibility. Thus far, our knowledge of spatial flexibility is limited to behavioural aspects and single neural activation. On the other hand, our understanding of hippocampal-declarative memory and spatial cognition have witnessed dramatic advances in recent years, providing provocative information about flexibility.

The hippocampal formation has recently been in the center of scholars' attention in regard to memory and navigation. In 2014 two significant hippocampal discoveries led to researchers winning the Nobel prize in physiology. First, O'Keefe and Dostrovsky (1971) identified nerve cells involved in the creation of the spatial map that enables the brain to navigate accurately. In mice models OKeefe observed the firing pattern of what has been named "place cells" when a rat reached a particular point of a given map. Other nerve cells were activated at different sites of the map and these place cells created an inner neural map in the hippocampus (Figure 1.9). Based on OKeefe's discovery, scientists believed that representation of the spatial map was solely generated in the hippocampus itself. May-Britt Moser and Edvard Moser extended the investigation to adjacent structures when they posited that major hippocampal input was received from the entorhinal cortex. In so doing, Mosers disconnected entorhinal-CA3 projection, and surprisingly, the CA1 developed regular place cells and performed normally during acquisition of spatial task. In contrast, mice failed to retrieve spatial

Figure 1.9: The grey square represents a free spatial task. Indicated dots demonstrate firing patterns of place cells when mouse approaches a specific site in the field. Adapted from Kiehn and Forssberg (2014).

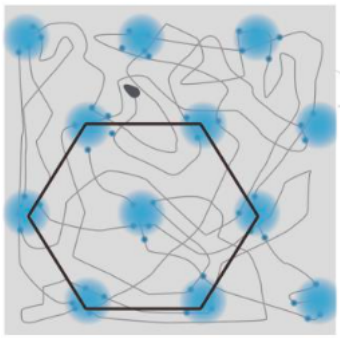


Figure 1.10: Blue dots indicate grid cells in the entorhinal cortex. Single grid cell activates when the mouse reaches a specific site in the field, while hexagonal form of firing grid cells is present throughout the map. Adapted from (Kiehn and Forssberg, 2014).

input. Findings suggest that there are two essential memory circuits: the entorhinal-CA1 projection for "recollection-based recognition memory" and the CA3-CA1 circuit to recall (Brun et al., 2002). Direct projection between the entorhinal cortex and CA1 has been further examined in the medial entorhinal cortex. Data has revealed a novel cell type - "grid cells"- in the medial entorhinal cortex, which showed unusual pattern of firing. During spatial tasks, grid cells display hexagonal activated nodes across the map (Figure 1.10). Grid activation plays a vital role in measuring distance and

orientation in metric navigation. Interference between place cells and grid cells refutes the hippocampal-independency hypothesis and reinforces a hypothesis of a division of labor and computation between the hippocmapus and entorhinal cortex (Hafting et al., 2005). Humans possess a relatively larger hippocampus and entorhinal cortex, which are central in human spatial cognition, and several studies have found homologous spatial-coding patterns of place-like cells activated at specific sites during navigation (Ekstrom et al., 2003; Jacobs et al., 2010), and grid-like cells in the entorhinal cortex (Jacobs et al., 2010, 2013).

Cognitive flexibility plays a pivotal role in navigational strategies that necessitate adaptation to altered stimuli in the environment. Thus far, PFC and basal ganglia are two regions implicated in behavioural adaptation and flexibility due to profound prefrontal projection to basal ganglia (Ragozzino, 2007). Indeed, the PFC has been assigned to higher executive functions, including flexibility (Fuster, 2001; Duncan, 2010). Nevertheless, I argue here that the hippocampal declarative function to large extent contributes to navigation and reversal learning. Mice with a lesioned hippocampus were introduced to a two-simultaneous-cue task. The first cue requires an established map of a maze based on specific locations and landmarks, in a grid cell firing fashion, whereas, the second cue required mice to rely on individualistic strategies based on body orientation. Results showed that flexible navigation was limited to the control groups, whereas insulted hippocampal mice displayed severed capacity and an inflexible "egocentric strategy" to reach the award (Ramos and Vaquero, 2000). In a water-cross maze, C57BL6/N mice failed in the relearning phase when response-basedbody-turn strategies can be utilized. On the other hand, place learning facilitates

spatial flexibility. Severely disrupted re-learning has been associated with a 60% reduction of hippocampal volume due to an ibotenic lesion, which suggests a significant importance of the hippcoampus in novel adaptation and strategy switching (Kleinknecht et al., 2012).

Fewer studies have investigated flexibility in the light of a simultaneous implication of the hippocampus and PFC, which ultimately requires profound connection in real-time processing. An established connection between both structures has been illustrated in other domains, such as memory consolidation (Takehara-Nishiuchi and McNaughton, 2008).

1.5 Aims and hypotheses

As we proceed from the classical point of view examining how it can be criticized from various aspects, current work aims to enlarge the map of the language network in the brain. For decades, the main focus of research has been devoted towards "language areas" in the cerebral cortex with a tendency to omit important roles played by other brain regions. In this thesis I hypothesize that hippocampal declarative memory critically contributes to online language processing via a complex mechanism of relational binding and flexibility, which integrates inputs from multiple sources to serve contextual situation demands. Despite the lack of literature but with the aid of previous work by Duff and Brown-Schmidt (2012) and Lee et al. (2017), I intend to emphasise the importance of the hippocampus in online language processing by discussing various issues in the core section of the thesis, followed by discussion of several neurodegenerative diseases and syndromes in which the hippocampus is largely affected and language is impaired. In-

deed, advances in hippocampal studies in other domains, such as memory and spatial navigation, are indispensable in the building of a decent hypothesis of the hippocampus and language processing. Furthermore, as will be discussed, segregation between language and memory has created a gap in our understanding of how the human brain processes language. I aim to emphasize that both work together in the process of language.

Chapter 2

Hippocampal function in cognition

2.1 Hippocampus and language

If we to look at the specific form of language, verbal real-time communication is remarkably unique to human language, and despite accumulated work on many aspects of language, online language processing remains a puzzle for linguists and cognitive neuroscientists. Human language possesses a system of infinite constructions along with a creative and flexible use of communication in particular contexts (Duff and Brown-Schmidt, 2012). During real-time language communication, speaker and listener perform rapid processes of generating, receiving, and integrating multiple resources while maintaining current representations along with the communication process (Duff and Brown-Schmidt, 2012). The flexibility of human language is manifest through highly complex biological foundations that other species lack. While considering the classical model of language, I wish to pose the ques-

tion of whether the traditional view of "language areas" within the brain is sufficient to explain flexibility as a human-specific language property. In the current chapter I present the issues and topics that serve to encourage the core proposal of a wider language network within the brain, including potential hippocampal contribution, a hypothesis that has largely been neglected by previous researchers.

The general orientation of the neurobiological field of language excludes subcortical regions. With a "corticocentric" focus, a few studies have attempted to extend the concept of the neural network of language within the brain with the aid of state-of-the-art techniques and brain imaging. Booth et al. (2007) have examined how the cerebellum and the basal ganglia contribute to the phonological processing of language. Findings have shown that the cerebellum is reciprocally connected with brain regions known to play roles in phonological processing, i.e. the inferior frontal gyrus and the lateral temporal cortex. Likewise, the basal ganglia have shown less and unidirectional connectivity to previous cortical regions during rhyming judgement tasks. Discussions of aphasia due to lesions in subcortical structures in the meta-analytic work by Alamri et al. (2015) suggest a relationship between aphasia and damage to the thalamus and basal ganglia. Specifically, the study's results showed that 110 out of 394 aphasic patients who had lesioned basal ganglia also displayed comprehension deficits, as did 31 patients out of 288 with thalamic lesions. Further, 129 out of 394 aphasic patients with lesioned basal ganglia exhibited naming deficits, whereas 12 out of 288 patients with lesioned thalamus were impaired in naming. And in recent years several studies have stated that the number of regions involved in language processing have been underestimated. One of the difficulties in assessing

the language network is that the human brain displays great plasticity. For instance, children with focal lesions vary in how their cognitive deficits are expressed compared to adults, which might be due to the greater functional plasticity in the child brain (Vargha-Khadem et al., 1994). Interestingly, to assess language lateralization, during a task that normally activates Broca's area, fMRI findings from epileptic children who have sustained early lesions in the left hemisphere indicate that a lesioned left Broca's area and adjacent regions were not associated with activation in analogous regions in the right hemisphere. However, subjects with hippocampal lesions exhibit right-lateralized, or bilateral, language-region activation. Regardless of capacity of classical model adjacent areas to process language, these findings highlight that hippocampal formation may determine language lateralization (Liégeois et al., 2004; Knecht, 2004).

Ullman (2001a) has put forth a declarative-procedural (DP) model of language processing. His model posits that language relies on two subsets of long-term memory: declarative and procedural memory. Both memories have been well documented at cognitive, and biological levels, which motivated Ullman to apply the model to first and second language processing. Briefly, the declarative memory system is responsible for learning, representation, general knowledge, memory of facts, and personal experience (Squire, 2004). The hippocampus is a major hub of memory formation, learning, and consolidation, and is included in this system. On the other hand, procedural memory is responsible for unconscious learning, motor and cognitive skills, and the execution of consequences of motor learning. The basal ganglia in concert with the frontal cortex underlies procedural memory processes (Eichenbaum and Cohen, 2004). Ullman (2001b) has proposed that differ-

ent aspects of language are associated to different neurocognitive systems. Based on the DP model, the mental lexicon is stored in declarative memory in the hippocampus, and mental grammar is computed in procedural memory in the basal ganglia and the frontal lobe. In other words, declarative memory maintains subcomponents of a mental lexicon, such as words and their meaning, irregular morphology, and irregular forms of verbs, while procedural memory applies rule-governed sequences of structures, such as regular verb forms of past, present, and future tenses.

Although, these memory systems are distinct, both cooperate and compete in learning processes (Poldrack and Packard, 2003; Schreiweis et al., 2014). In animal studies, hippocampal lesion enhanced procedural learning in the basal ganglia (Schroeder et al., 2002). In humans, a large body of evidence supports the DP model of language processing. fMRIs report activation in the left hippocampal and parahippocampal gyri during semantic tasks (Newman et al., 2001). Specific language impairments provide solid evidence of grammatical impairment and the dysfunction of procedural memory underpinnings (Ullman and Gopnik, 1999). Aphasia is the prime source of evidence gathered in the Broca's-Wernicke's model, with non-fluent aphasia findings often indicating a damaged Broca's area and basal ganglia lesion (Damasio, 1992; Dronkers et al., 2000). In the neurodegenerative diseases Alzheimer's, the disease targets the hippocampus in early stages, while the basal ganglia and Broca's area often remain healthy. Generally, AD patients are incapable of acquiring new words or retrieving stored lexical items (Ullman, 2004).

Ullman's model is one of a number of proposals that reinforce the importance of the medial temporal lobe in the brain's language network. Cognitive and clinical evidence for this model are increasing, but what is needed is further examination of the patterns of the non-linguistic aspects in declarative and procedural systems in order to develop a DP model for the subcortex.

Another important hypothesis, and one which inspired my proposal, expresses a specific hippocampal contribution to language. Human language characteristically displays an unlimited range of expression and creativity. One of the issues that remains challenging in the study of language processing is online language communication and the high level of flexibility that occurs during social interaction, which is manifest in the rearrangement of structures based on current context. This kind of process requires a high level of cognitive flexibility and creativity. Cognitive flexibility refers to rapid adaptations, dynamic activation, and the modification and shifting of processing according to specific stimuli. Chomsky (1975) noted that creativity is a unique phenomenon of human language. One can be exposed to a limited set of "utterances" in a language, and still show high competence in creating an infinite range of new phrases based on a limited, acquired set.

Duff et al. (2008) propose that online language processing and social interaction receive a fundamental contribution from hippocampal declarative memory via a relational-binding mechanism. This current hypothesis is innovative in the context of language processing and the neurobiological modelling of language. Traditionally, the hippocampus has been associated with lexical storage, as Ullman (2001b) has speculated. In current hypotheses, however, episodic memory enhances the flexibility and creative

use of language. Several findings from amnesic patients suggest a short-lag in cognitive flexibility tasks. Amnesia is a memory deficit condition caused by damage to memory substrates in the brain (Parkin, 1997). Likewise, the hippocampus is critical for creative thinking (Duff et al., 2013), and for creativity in nonhuman animals (Kaufman et al., 2011). Findings from amnesic patients show relational memory deficits and short delays in spatial and non-spatial tasks (Hannula et al., 2006; Hannula and Ranganath, 2008). Findings from Duff et al. (2008) show that hippocampal amnesic patients uttered less verbal play compared to control groups. By contrast, verbal play remained intact in the case of a damaged ventromedial prefrontal cortex (Gupta et al., 2012). Language and memory have been typically segregated, and noteworthy, the mechanism in which the hippocampus serves online language processing is related to memory formation and relational binding, or arbitrary items that are essential to carry out communication. The neurophysiological mechanism that engages the hippocampus is as yet unknown. Nevertheless, theta-oscillation measurements suggest that the same hippocampal neural computation for memory serves online language processing. Piai et al. (2016) argue that theta activation observed in the hippocampus is associated with the on-going relational processing of incoming words to previously stored semantic knowledge. Recent fMRIs have produced intriguing findings, detecting hippocampal activation during linguistic tasks associated with activated cortical language areas (Blank et al., 2016).

Based on the major discoveries of "place" and "grid" cells, which both facilitate spatial navigation (see introduction), from O'Keefe and Dostrovsky (1971); Hafting et al. (2005) suggest that hippocampal-entorhinal circuits

create a hexagonal mental map of physical space in navigation, based on multiple variables including the location in the maze, head direction, and speed. Advances in understanding the hippocampal-entorhinal contribution to spatial cognition present a single mechanism of a cognitive domain among others in the hippocampus. Nevertheless, recent studies have tested the speculation that place and grid cell types may not be specific-navigation cells. In so doing, Constantinescu et al. (2016) used fMRI technology to investigate if humans use "hexagonally symmetric code" in abstract conceptual representations, as occurs in physical navigation. Results have shown a hexagonal network that anatomically resembles the network activated during physical navigation (Jacobs et al., 2013), including the entorhinal cortex and default mode network regions, such as the cingulate cortex. Taking a wider perspective, Aronov et al. (2017) suggest that the mental map of spatial representation is a general hippocampal mechanism that accommodates other cognitive domains. Results from their sound-manipulation tasks indicate a shared role in the hippocampal-entorhinal system, with spatial tasks and a common mechanism of encoding spatial and non-spatial performances. Taking into account the associative and relational function of the hippocampal formation, findings have shown that relationships of non-spatial, discrete items were supported by hippocampal-entorhinal metric representation, akin to a grid-cells pattern of firing during physical space tasks (Garvert et al., 2017).

On the other hand, the hippocampal declarative memory system is not segregated from social cognition. More attention has been paid to personal and episodic memory, as memory governs our interactions and expectation during social interaction with others by binding discrete information. Never-

theless evidence coming from hippocampal amnesia suggests intact linguistic ability, even in amnesic patients who exhibited a deficit in the interactional aspects of social communication and flexibility (Duff et al., 2008). Rubin et al. (2014) suggest that, along with the frontal lobe, which has been largely associated with flexibility and executive functions, the hippocampus is also essential to flexible cognition and representation in a complex dynamic of social interaction that demands an appropriate selection of words towards familiar and unfamiliar individuals. Although amnesic patients are impaired in social interactions, it would be possible for grid-like hippocampal cells to act in a similar manner, creating a mental map of social cognition based on previous knowledge of individuals, which permits the information to be processed based on real-life situations. Previous findings of hippocampal-entorhinal implication during goal-directed behaviour and non-spatial tasks pose a notion of a more general role played by grid cells in which online language processing receives a major contribution.

2.1.1 Relational binding

A wide range of cognitive domains is attributed to the hippocampus. The hippocampus has long been acknowledged as supporting spatial navigation, initiating memories, building arbitrary semantic relations between items and meanings, as well as episodic memory. In addition to navigation, a major focus of hippocampal research has been oriented towards one type of relation, namely, long-term memory. The capacity humans possess to bind many fragments of information to serve a single context is known as "relational binding", and may indicate the interconnection of hippocampal functionality across various cognitive domains. For instance, humans are able to initiate

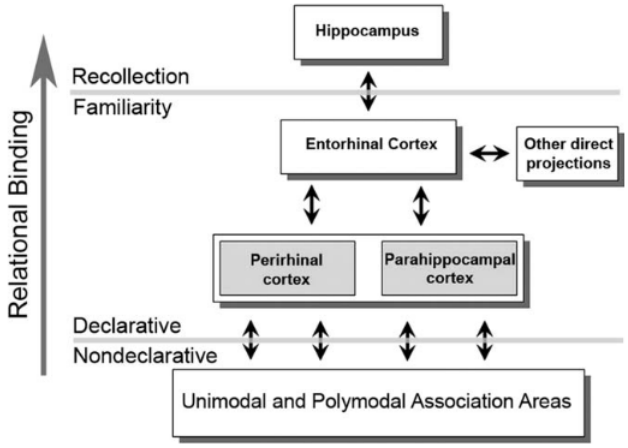


Figure 2.1: This schematic model of MTL heirarchy indicates the central role of the hippocampus in relational binding. Edited by (Shimamura, 2010) and adapted from (Lavenex and Amaral, 2000).

real-time communication in a novel context based on previously stored units of information. Likewise, the concurrent integration of various elements facilitates the comprehension of meaning. Given that memory is principle in online language use, the fact that research literature treats memory and language in isolation seems inadequate.

Undoubtedly, the hippocampus is one of the most investigated regions in the mammalian brain. However, one of research's most challenging questions is, to what extent can we extract a model of hippocampal contribution to language? The growing body of evidence from comparative studies and amnesic patients suggest that the hippocampus plays a pivotal role in the formation of relational binding (Figure 2.1). Hippocampal amnesic patients show impaired capacity to bind multiple elements or to retrieve associations (Yee et al., 2014; Watson et al., 2013). A rich literature provides us with compelling evidence of the multiple cognitive domains executed via the

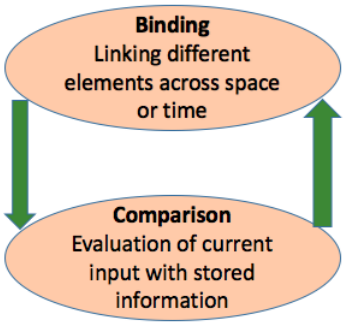


Figure 2.2: Basic model of the hippocampal function of comparison of contextual input and relational binding of various elements to perform multiple cognitive domains.

hippocampus. However, there is no clear understanding of the mechanism behind how the hippocampus coordinates across multiple cognitive domains, whether in a single flexible or cognitive-dependent process. To support my proposal, I have focused on relational memory in order to indicate the critical role of the hippocampal declarative memory system that goes beyond navigation and long-term memory. In doing so, my theoretical frame will take into consideration two functions. First, a comparison and evaluation of contextual input with previously stored information, and, second, the binding of various elements across time or dimensions, which project to the hippocampus from other more remote regions in the brain (Figure 2.2). In order to gain a wider perspective of the functional mechanism, the paper's examination of declarative memory will be divided into several parts each of which examines different phases of memory. To begin with, activation of declarative memory retrieves a network of relevant items through which we possess a multi-access system to a single memory. An interesting example by Eichenbaum (1993) indicates three potential performances of the declarative memory. In a given situation of, say, reading a new book, the hippocampal memory system is provoked to store selected information about

the book, including the title, particular words, phrases, illustrations, and to associate these to related previously stored knowledge. Likewise, the context and circumstances that occur during the action of reading might be stored relationally. In other words, the hippocampal declarative memory engages from basic cognitive levels to more complicated ones. At first level is basic "reinstantiation" and retrieval of the principle information of the book and recognition of its notions when represented. At the second level is the retrieval of detailed information and the contents of the book in an isolated context from the original acquisition for demonstration purposes. Third, the hippocampal declarative memory adds to the flexible use and manipulation of the stored information about the book in various processing models, comparisons, and new contexts.

The third phase is fundamental to real-time language processing, but is the least tackled in the research of the subcortical level. For instance, the memory, unification, and control (MUC) framework developed by Hagoort (2003, 2005, 2013) proposes that language processing is comprised of the following: 1) memory, which stores and retrieves language information in the long-term memory; 2) unification, which integrates a retrieved lexical item into valid representation in the context, and 3) control, which translates the process into action. Regardless of the confusion created in the division of labour between the terms memory and unification, the framework deals with memory at a very basic level, namely, storage and retrieval. Whereas the "unification operation" is a higher cognitive level performed by hippocampal declarative system. Regardless of fundamental subcortical roles in memory, the MUC framework dedicates previous components, including the unification operation, to the Broca's area to serve online language processing. This

follows the traditional conceptualization of Brocas area function.

Needless to say, this thesis's proposed expanded perception of hippocampal function does not impose an independent role for language but rather a cooperative role with various cortical regions including the prefrontal cortex. The hippocampus can be seen as binding scattered information from other co-activated cortical regions, which in part means that the hippocampus does not accommodate stored information, which is agreement with findings that indicate this major contribution is from the PFC (Braver et al., 2001; Badre and Wagner, 2007).

Several properties are in favour of the hippocampus having the neurobiological function of flexibly mediating multiple elements of remote regions. In this regard, two properties of the hippocampal synaptic mechanism especially should be taken into account. First, inputs arriving at the hippocampus cause a stable increase in synaptic transmission that lasts for hours, days, or weeks, and is known as long-term potentiation (LTP). The molecular and cellular mechanisms associated with LTP suggest the hippocampal capacity of binding various elements (Morris, 2006; Lüscher and Malenka, 2012).

Research in spatial navigation in the hippocampus has witnessed exceptional advances, which can be exploited to shed light on other hippocampal cognitive procedures and to better our understanding. For instance, "place cells" display specific patterns of firing depending on location, occupation, and movements by animals, and our understanding of the specific function of these cells has been augmented by the recent discovery of "grid cells".

Place cells were thought to be independent from animal orientation within the space field (O'keefe and Nadel, 1978). Contrasting findings of place cells alteration corresponding to changed rotations of place cells except the shape (Muller and Kubie, 1987; Muller et al., 1987). Previous findings gave rise to questions of the characteristics of hippocampal complex-spike cells in spatial navigation. Eichenbaum and Cohen (1988) argue whether place is the principle variable in hippocampal complex-spike cells during spatial activity. Based on previous experiments, animals were sensitive to other variables, including speed, direction and movements across the place field. In addition, complex-spike neurons exhibit relation function among spatial and non-spatial stimuli (Wible et al., 1986; O'Keefe, 1999). Compelling evidence indicates that place is not the only determinant of complex-spike neurons, and Eichenbaum and Cohen (1988) suggest that the term "place cells" limits the encoding of the hippocampus; rather, the term "relational cells" adds a wider range of critical cues as to their relations within a cognitive task.

Eichenbaum and Cohen's criticism provokes discussion about the relational aspects that exist at the neurological level. An important hippocampal pattern of oscillations are designated sharp wave ripples (SWR) (Figure 2.3), and are composed of large-amplitude sharp waves recorded during sleeping state (Maier et al., 2013). SWR reactivate an awake experience during slow-wave sleep, supporting the consolidation of memories and the transfer of memories to the neocortex (BuzsÁk, 1998; Mölle et al., 2006). After spatial navigation tasks, mice with disrupted neural activity related to ripples in post-task rest state display major impairment in spatial learning compared to healthy controls (Ego-Stengel and Wilson, 2010).

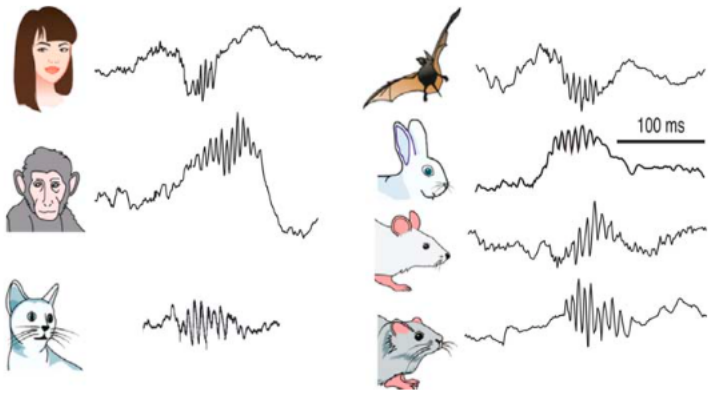


Figure 2.3: SWRs have been observed in various mammals. The illustration shows SWRs across several species. From (Buzsáki et al., 2013) and (Buzsáki, 2015).

Although the basic function of SWR is memory consolidation via the offline reactivation of hippocampal neural ensembles, several recent studies observed SWRs firing during awake episodes (Kudrimoti et al., 1999; Jackson et al., 2006; Jadhav et al., 2012). In animal navigation, SWR fire between place fields points during pauses in movement. While the task demands a high level of relational binding and flexibility, interpretations suggest that SWR improve performance by reactivating previous place cell assembles, and may aid in binding novel spatial features in current tasks (Sadowski et al., 2011). "Remapping" phenomena indicate a greater rate of hippocampal flexibility. Dupret et al. (2010) observed CA1, but no CA3, in the reactivation and remapping of place cells, which suggests that the CA3 contains fixed representations, whereas the CA1 exhibits adaptive behaviour towards new spatial information.

In light of the "relational cells" concept and recent work on SWR online firing, it is possible that SWR empower performance in spatial and other higher cognitive tasks. Yet, the precise function and mechanism warrant fur-

ther investigation and demonstration to account for other cognitive domains and language processing.

2.1.2 Neural binding

Online language processing is not a trivial task. Speakers and listeners perform a multi-component process of combining, recombining, generating, and maintaining representations. To better understand the hippocampal contribution to the process I herein put forward another idea at the neurobiological level. The hypothesis of neural binding suggests that neural signals coordinate via synchronized oscillations during neural activity, combining and recombining to flexibly process stimulus-related information (Senkowski et al., 2008). The reason to adapt neural binding is due in large part to the relationship between neural binding theory and gamma oscillation to illustrate synchronization of activation across scattered brain regions. Similarly the current hypothesis proposes the hippocampus contributes to real-time language processing in concert with other brain regions including the PFC.

As to the importance of gamma oscillations in the brain, the classic work by Gray et al. (1989) yields important findings of gamma oscillations that underlay synchronization of inter-columnar input in the cat visual system. Further investigation highlights the gamma oscillatory role in spatial navigation and working memory; during a T-maze spatial task, mice show that hippocampal gamma oscillations in several subregions are triggered at certain locations where mice needed to retrieve information in order to select given routes (Montgomery and Buzsáki, 2007). Although, there is no current solid model of its substrates, neural binding has been diagnosed as a "problem" (Feldman, 2013). Neural binding is traditionally linked to the theme of

binding problems in visual perception and other multisensory processes when understanding the underlying mechanism of coordinating multiple resources (Treisman, 1996; Roskies, 1999; Burwick, 2014). Indeed, neural binding in the context of multisensory perception encounters several obstacles, including the absence of a defined model of specific cortical/subcortical structures and their connections based on anatomical findings. The subjective unity of perception and its correspondence to one's experience, and the coordination of remote regions and circuits may appear temporally synchronised with no further demonstration (Feldman, 2013). Unlike previous issues in multisensory binding, our assumption of hippocampal relational binding in language processing seems to be an endogenous activity (top-down approach) examined for various reasons. First, neural binding relies largely on gamma oscillations (30-100 Hz frequency range) to measure neurophysiological correlations distributed through the cortical layer and including the frontal and occipital lobe (Müller et al., 2001). Second, in the hippocampal formation there are three well-characterised oscillations theta, gamma and SWR all of which occur in the neocortex (Butler and Paulsen, 2015). Gamma oscillations in the hippocampus indicate a lower amplitude than theta oscillations and SWR, therefore, and less experimental attention has been devoted to gamma oscillations in the hippocampus than to theta rhythms and SWRs, but here we consider gamma waves of particular importance in higher cognitive processes. For instance, memory and relational binding require a dynamic coordination of remote regions in the brain. Third, gamma-frequency activity also plays an important role in working and declarative memory (Jensen et al., 2007), including that of the PFC (Benchenane et al., 2011).

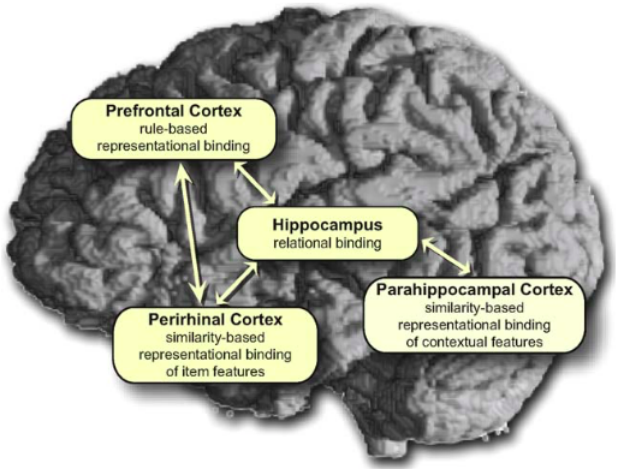


Figure 2.4: Distributed hippocampal-cortical network of relational binding contribution to online language processing. The hippocampus appears to be central of various cortical information resources, Adabted from (Opitz, 2010).

Due to the dynamic nature of relational binding, one can speculate that high-frequency gamma oscillations are a feasible tool for providing key understanding of distributed cortical-hippocampal engagement in online language processing with millisecond range precision (Figure 2.4). Hippocampal gamma oscillations are ideal for carrying out higher cognitive processes that demands fast neuronal coordination, such as grouping neurons into functional ensembles and memory retrieval (Colgin et al., 2009; Csicsvari et al., 2003). Hence, we assume that gamma oscillations may effectively indicate the rapid temporal dynamics of synchronization between remote brain regions, namely, the hippocampus and the PFC. Predection within social interaction and communication is crucial during real-time language processing. Interestingly, findings have revealed a relationship between gamma oscillations and sematic unification. Hald et al. (2006), observed gamma increased power in the right frontal areas when a highly expected word occurred within a sentence (e.g., "The Dutch trains are yellow and blue"), but not when the

sentence contained a semantic violation (e.g., "The Dutch trains are sour and blue"). Likewise, Rommers et al. (2013) have indicated that, in sentence processing, unexpected words triggered medium gamma power. Later studies found gamma power activation during normal online language processing in instances when expectancy played a role, while gamma oscillations tended to be disrupted during semantic violations. While previous studies focused on oscillatory activation in frontal areas, findings from Sederberg et al. (2007) have revealed that gamma oscillations (44-64 Hz) in the hippocampus, the left temporal, and the frontal lobes predicted the successful encoding of new verbal memories.

There is a growing body of literature studying the relationship between oscillatory neural dynamics and sentence-level language comprehension.

Although, theta and gamma waves are separately generated, both oscillations co-occur within the hippocampus, however, while theta oscillations are more stable during cognitive processing, gamma oscillations can display sudden high activation within theta waves (Stumpf, 1965). Interregional gamma oscillations are also independently generated in two hippocampal regions: in the dentate gyrus, which depends on entorhinal cortex input, and in the CA3 extended to the CA1 (Bragin et al., 1995). The CA1 exhibits various types of gamma oscillations (Figure 2.5): lower frequencies ranging 25-55Hz are termed "slow gamma" and higher frequencies ranging between 60-100Hz are known as "fast gamma" (Colgin et al., 2009). Though both forms of gamma oscillation differ in cognitive functions, the majority of experimental work has been carried out on spatial navigation models of animals. If slow and fast gamma oscillations contain distinct network states,

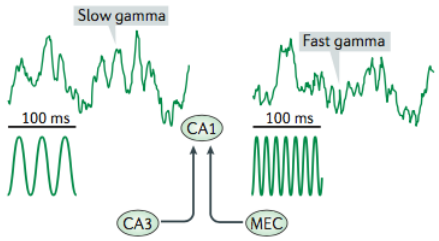


Figure 2.5: Two distinct forms of gamma oscillations, slow and fast, occur in the CA1. Slow gamma oscillations couple with input from CA3, whereas, CA1 fast gamma oscillations are entrained by the medial entorhinal cortex. Cridted to (Colgin, 2016).

it is possible that each form serves a different behaviour. Several studies extracted variations that might be of help in the context of memory and online language processing. Attempts to identify differences between fast and slow gamma oscillations rely on trajectory signals. Fast gamma driven by medial enorhinal cortex sensory inputs enhance the process of memory encoding in mice (Newman et al., 2013). Other evidence suggests that fast gamma oscillations are associated with an alteration of physical behaviour; for instance, the increase of fast gamma oscillations along with the speed rate of mice (Zheng et al., 2015). On the other hand, slow gamma oscillations are hypothesised to boost memory recall. Given that CA1 slow gamma oscillations are entrained by CA3, and accumulating evidence of CA3 being a memory storage hub, current hypothesis tends to be feasible (Nakazawa et al., 2002; Treves and Rolls, 1992). Interestingly, Bieri et al. (2014) found that slow gamma in mice enhanced memory retrieval of spatial sequences and prediction of upcoming locations in the place field, whereas fast gamma underpinned recent location encoding.

In the context of language processing, Hagoorts MUC framework by (2003, 2005, 2013) suggests an online "unification function" that allows flexible lan-

guage processing at the cortical level. However, several studies have observed increased gamma oscillations during semantically coherent and predictable sentences. To identify the functional significance of gamma oscillations during online language comprehension, (Wang et al., 2012) examined gamma synchronization in word prediction tasks based on prior sentence context. Furthermore, in multiple experiments, Nieuwland and Martin (2017) reported an engagement of the subcortex via increased cortico-hippocampal gamma oscillations during online sentence comprehension of referentially coherent phrases compared with referentially problematic ones.

Cross-frequency coupling is another interaction of oscillation modes within the hippocampus. While early studies have focused on a single form of oscillation, recent cognitive neuroscience tends to be attracted by the complexity of cross-frequency coupling and its functional consequences. General speculation is that theta-gamma oscillation coupling in the hippocampus underpins learning processes. Tort et al. (2009) showed that hippocampal slow gamma oscillations are boosted by a theta phase during mice spatial learning processes. And theta-gamma oscillation coupling showed a positive correlation with performance accuracy and adaptation to contextual alterations of food reward. Likewise, Shirvalkar et al. (2010) suggest that cross-frequency correlations in the hippocampus are crucial for memory-guided behaviour in mice, not only in behaviour dependent on long-term memory but also in working memory (Axmacher et al., 2010). Evidence from Maris et al. (2011) has revealed wide spatial maps of the coupling oscillations including hippocampal activation and suggests theta-gamma coupling maintains short memory in online information processing, Lisman and Idiart (1995) indicating "that activity patterns associated with multiple memories can be stored

in a single neural network that exhibits nested oscillations similar to those recorded from the brain". These findings mesh well with other findings of entorhinal cortex facilitating storage of recent past and prediction of the future (De Almeida et al., 2012). Previous evidence of spatial cognition and memory in animal models concludes that theta-gamma coupling is essential in memory encoding and, more importantly, in prediction during performance. The latter function is an influential factor that can be speculated as critical in online language processing.

Synchronization on a large-scale level should also be taken into account. As gamma oscillations occur locally, there is little evidence suggesting a remote gamma oscillation synchronised network. Nevertheless, slower oscillations reflect encompass more neurons (Von Stein and Sarnthein, 2000). I suggest that the hippocampus and online processing could tap into hippocampal-cortical synchronization. Although, theta synchrony is the dominant mode representing prefrontal contribution to the hippocampus, theta-gamma oscillations should yield a clear understanding of such interplay during online language processing.

To identify dynamic integration of language production at the cortical level, Liljeström et al. (2015) observed alterations in gamma oscillations in the bilateral prefrontal cortex, the medial frontal cortex, and the posterior middle temporal gyrus during the early time window, which may indicate a modular cognitive mechanism. However, in verbal memory formation, Sederberg et al. (2007), focused on gamma oscillations of 44–64 Hz in the hippocampus, the left inferior prefrontal cortex, and the left lateral and medial temporal cortices to predict new verbal memory formation. Previ-

ous evidence had indicated hippocampal gamma activation during language tasks. Likewise, Meyer et al. (2005) showed gamma activation in the hippocampus to underlay processes of syntactic integration in language comprehension tasks. And although fMRI studies may effectively provide us with a clearer image of the process, event-related potentials are necessary to highlight distributed neural networks and electrical activity linked to the hippocampal capacity for combining many inputs from different cortical regions in real-time language processing.

2.1.3 Verbal communication

Studies of the neurobiology of language have been more directed towards language aspects individually and the identified boundaries between those aspects. Although previous approaches merit special attention in traditional literature, other models are of interest in removing experimental boundaries and exploring hypotheses outside classical conceptions. Verbal communication as a joint activity between speaker and listener is a genuine model for highlighting the contributions from scattered brain regions, including the subcortex. It imposes a novel manner of observing multi-brain coupling during communication. The brain-to-brain coupling approach (Figure 2.6) is comprised of three fundamental components. First, linguistic knowledge. Second, social cognition of various processes that need to deal flexibly within a context (Frith and Frith, 2007; Frith, 2008). And third, memory of a common ground during interaction. Speaker and listener share online interaction, and both brain activations display spatial and temporal synchronization which disappear with communication failure (Stephens et al., 2010). Previous findings are in sync with the theory of interactive linguistic align-

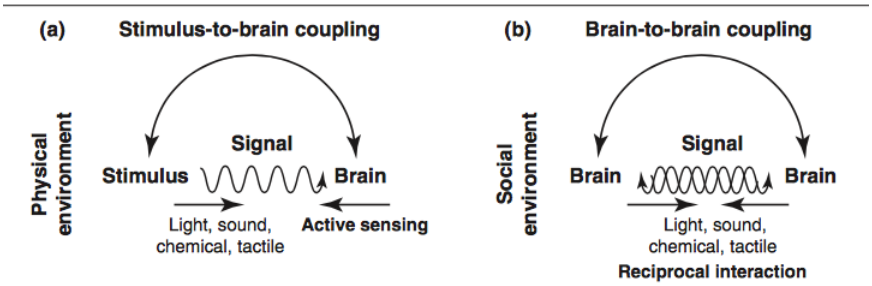


Figure 2.6: Model of (A) physical and (B) social environment coupling during social interaction. From (Hasson et al., 2012).

ment, suggesting that verbal communication generates alignment at various levels, including phonetic, phonological, lexical, semantic, and syntactic representations (Pickering and Garrod, 2004). However, neural observation has been directed towards cortical structures including "language areas" during different processes (Stephens et al., 2010). For instance, the precuneus medial prefrontal cortex (mPFC) has been activated as an "extralinguistic" region during online speech comprehension (Lerner et al., 2011).

Though the neocortex has gained more attention, recent studies reveal intriguing fMRI findings from Silbert et al. (2014), which concluded that the right hemisphere is activated during online language processing. Unlike other short sentence production tasks, current study aims to assess the prevalence of activation during long, unconstrained online narrative. With no subcortical consideration, the left medial temporal gyrus (MTG) appears to be critical for lexical retrieval. Bilateral activation has been associated with the MTG, the superior temporal sulcus (STG), and other "linguistic" and "extralinguistic" regions, such as the mPFC, which has been labelled as a hub of social cognition understanding and interpretation during verbal communication.

I speculate that verbal communication experiments will mesh well with my proposal of hippocampal contribution in online language processing. Regardless of the cortical orientation favoured in current literature, hippocampal formation has to be included in the observation circle for two fundamental reasons. The first reason to consider the hippocampus as an important aspect of verbal communication is, as mentioned previously, social cognition. In concert with higher-cognitive function in the mPFC, the hippocampus is critical for human-specific social cognition during interaction. Social cognition implies an extensive amount of flexibility within communication, and social interaction requires an optimal use of relational memory and flexible cognition, including prior knowledge, recombination, adaptation to novel information, and manipulation. For instance, within a context of social interaction, our use of information, words and phrases, and behaviour highly depend on the familiarity of others, common knowledge, and on-going interaction and preferences (Rubin et al., 2014).

The role of the hippocampus does not imply discrepancy with the long-standing dogma of PFC executive function, or with the important contribution of working memory; evidence from PFC-damaged patients affirms social cognitive deficits, lack of coordination, and flexibility (Stuss and Levine, 2002; Alvarez and Emory, 2006). Nevertheless, there is compelling evidence that the hippocampus shares the labour with the PFC in flexible cognition. On the other hand, amnesic patients are capable of maintaining basic conversation in a social context (Rosenbaum et al., 2005), although other evidence has indicated social cognition disruption in amnesiacs, which includes the establishment and maintenance of social bonds. Davidson et al. (2012) examined social relationships and interactions in three amnesic pa-

tients, and their findings revealed a decrease in social network and social bonds from the onset of amnesia due to a lack of interaction and relational memory impairment. Likewise, patients with hippocampal damage tend to produce less reported speech and verbal play in their social interactions, which highly demands memory knowledge and flexible language use (Rubin et al., 2014).

The second reason to take the hippocampus into consideration in verbal communication is the significant facilitation involving prediction. As hypothesised by Stephens et al. (2010), cortical neural coupling in comprehension is greatly supported by the ability to predict upcoming words during online interaction. Regardless of linguistic studies of sentence constraints and how that may enhance words prediction (Schwanenflugel and Shoben, 1985), upcoming word prediction is tied to the hippocampal declarative memory system. The traditional standpoint holds that the hippocampus is a structure that retrieves memories from the past. Recent findings posit that the hippocampus is essential in memory-based prediction and imagination.

When trying to determine if amnesic patients are able to imagine new experiences, Hassabis et al. (2007) and Klein et al. (2002) found that amnesic patients were impaired in imagining new experiences. To firmly interpret findings in comparison to the PFC, Kurczek et al. (2015) examined patients with bilateral hippocampal damage versus patients with bilateral mPFC damage in studies of the narrative construction of neutral cue words during several time periods: real Past, Imagined past, Imagined present, and future. Interestingly, hippocampal-damaged patients showed deficits in reconstructing events during given periods, including the imagination of

future experiences. In contrast, mPFC-damaged patients and healthy controls were able to reconstruct events, and participate in future prediction. Previous findings provide insights into the nature of the essential neural mechanisms of the hippocampus to execute prediction/imagination by recombining fragments of previous memories into coherent scenarios (Addis and Schacter, 2012).

The two reasons discussed above concern the neural mechanism of online language processing and extend the verbal communication network to the hippocampus. Language is not independent from other crucial higher-level cognitive faculties. Herein lies the rub: boundaries created by linguists between aspects of language, such as lexicon, semantics, and syntax, cannot be precisely applied in the empirical research of the neurobiology of language. However, researchers speculate that successful online language processing cannot be done without integration and prediction. Integration implies the combination of those language aspects - lexical, syntactic, semantic and contextual inputs along with the ability of prediction, which gives rise to a higher level of anticipatory pre-activation of words based on given contexts. Both integration and prediction are interwoven in a chicken-and-egg fashion. Integration gives rise to prediction and prediction facilitates the integration process of upcoming words. To remedy the situation and in order to obtain a clearer understanding of language processing long-standing dogma needs reformulation by characterizing the underlying neural mechanism of integration and prediction as principles of human language.

The prominent role of prediction in online language processing leads us to the theory of mental time travel (Figure 2.7). The theory posits that

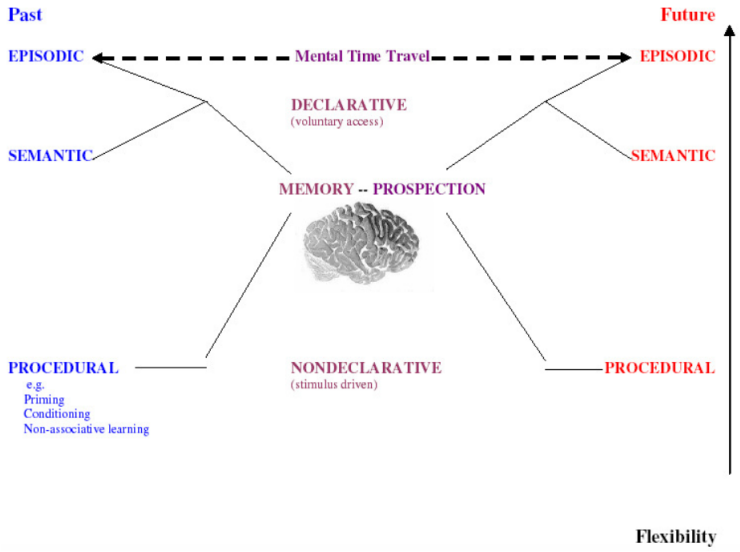


Figure 2.7: Mental time travel theory indicates flexible memory that enables humans to anticipate future events. From (Suddendorf and Corballis, 2007).

humans possess the capacity to recall past events and give predictions of future ones (Suddendorf and Corballis, 1997, 2007).

Mental time travel has been associated with the evolution of human language and is considered an ability that other species lack Corballis (2013), Significantly, it is one in which previous events are stored via hippocampal activity. Amnesic patients with bilateral hippocampal damage display difficulties in predicting future events (Andelman et al., 2010). Regardless of its philosophical dimensions, the theory highlights an important feature of social interaction and verbal communication in humans and one which is attributed to hippocampal declarative memory.

2.1.4 Default mode network

The default mode network (DMN) is a set of brain regions and neural networks activated during rest states and an internal mode of cognition, not only in rest state but also as one that contributes to thinking about past memories; anticipating the future; self-referential, narrative processing, and mind-wandering (Spreng et al., 2009; Simony et al., 2016). The DMN is constituted of remote brain regions including the parietal lobe and hippocampal formation (Vincent et al., 2006). Despite the interconnectivity between the hippocampus and DMN, less attention has been paid to the DMN's potential contribution to language. In this subsection I aim to shed light on a few issues that seek more attention from scholars and researchers in regards to hippocampal contribution to language.

The posterior cingulate cortex and ventral anterior cingulate cortex are core to the DMN with great activation during rest states (Greicius et al., 2003). Observations of various approaches in the identification of DMN brain structures suggest the MTL, mPFC and hippocampal formation are implicated (Buckner et al., 2008). During language comprehension, integrating input to previous knowledge takes place. Although the DMN is considered to be active during rest states, it may be involved in information processing during wakefulness (Hutchison et al., 2013). Studies have used inter-subject functional correlation to segregate correlation patterns of the DMN that were linked to the processing of each narrative segment and devoted to its meaning during narrative context, and, likewise, DMN coupling enhanced predicted memory of narrative segments (Simony et al., 2016). Findings focused on the DMN and language processing are scarce, however,

it does not imply that DMN ordinate with other brain regions during language comprehension and its interplay with other subcortical strucutures warrant further investigation.

2.1.5 Dopamine and the hippocampus

In an overview of hippocampal studies concerning memory, it is notable that major attention has been dedicated to the hippocampal capacity to store and consolidate past memories, but less attention has been placed on the investigation of the predictive properties of the hippocampus. As is characteristic of contemporary neurobiological theories of language, the language model by Ullman (2004) underscores a hippocampal/basal ganglia storage function that serves language. My proposal, however, recognises the significant role played by memory in relational binding and predictability in the context of online language processing. The hypothesis of hippocampal contribution to language flexibility and creativity expresses an excellent example of research that goes beyond traditional work in language in the brain.

In the current subsection I attempt to provide further explanations, at the neurotransmission level, of the potential role the hippocampus could play in language processing through adapting selected memory to serve context and upcoming words. The neurotransmitter dopamine is manufactured in the substantia nigra and the ventral tegmental area (VTA) and is a chemical released by nerve cells which sends signals to other nerve cells. The substantia nigra and VTA in turn project to the striatum, cingulate cortex, hippocampus, amygdala, and PFC (Figure 2.8). To release presynaptically, dopamine

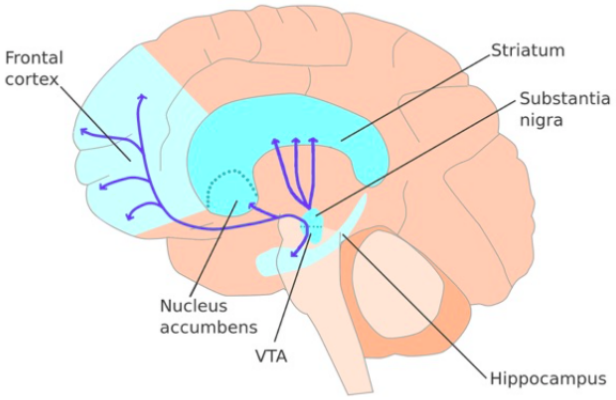


Figure 2.8: Main dopamine pathways in the brain. As illustrated, dopamine is produced in nerve cell bodies in the VTA and the motor dopamine function in the substantia nigra.

encompasses five receptors to interact with D1, D2, D3, D4 and D5 and all receptors are encoded by the genes DRD1, DRD2, DRD3 ,DRD3, DRD4 and DRD5 respectively. Dopamine is involved in reward-motivated behaviour, addictive behaviour, and motor controls (Seeman, 1980; Seamans and Yang, 2004). (Figure 2.8). , and is associated with reward prediction and memory adaptation for upcoming behaviour based on previous experience (Schultz, 1998; Shohamy and Adcock, 2010). To sketch the relationship between my proposal and current studies, several studies of memory and other cognitive domains in which dopamine seems to play a role are reviewed.

As illustrated in Figure 2.8, VTA dopamine neurons send direct signals to the hippocampus (Gasbarri et al., 1994). In animal models, dopamine at hippocampal synapses is present in LTP and learning tasks (Frey et al., 1990). Other evidence has found that VTA dopamine is highly activated in par with the hippocampal during the encoding of novel objects more than familiar ones (Schott et al., 2004). These findings were later developed into an important theory of a hippocampal-VTA loop that carries novelty inputs from

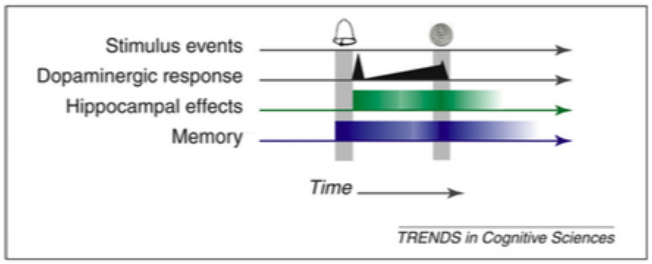


Figure 2.9: This time scale of dopamine modulation during memory processing illustrates speculation of hippocampal and dopamine activation in parallel with stimulus event and memory itself. Used with permission from Shohamy and Adcock (2010).

the hippocampus to the VTA "where it stimulates the novelty-dependent firing of these cells" and the inputs are stored as long-term memory (Otmakhova et al., 2013). It is important to note that dopamine neurons play an important role during the temporal stages of memory processing. For example, in rat studies, findings reveal that midbrain dopamine generates a synapse-specific underpinning of early LTP (Otmakhova and Lisman, 1996). To understand the anticipatory mechanism of reward-motivated memory formation, humans were able to recall cues indicating high value rewards during post training, and, interestingly, a pre-activated hippocampal-VTA loop during high-reward cues encoding enhanced post-training predictions (Adcock et al., 2006). Mice exhibit dopamine-enhanced associative long-term memory during a 24-hour period, not only during memory formation but also within consolidation phase (Bethus et al., 2010).

Indeed, the dopamine modulation of memory has motivated researchers to probe relevant domains, such as creativity and language processing, in detail. Taking into account the dopaminergic system, the hippocampus and the PFC, Wong et al. (2012) hypothesize that dopamine-related genetic variations might be related to language-learning differences. This hypothesis

seems to benefit from the previous model by Ullman (2001b), which suggests a prominent role of procedural memory in grammar learning. Given that the neural bases of procedural memory rely on the basal ganglia, the proposal of frontostriatal genetic variations by Wong et al. seems to be a promising path for research. My proposal, on the other hand, tends to pay close attention to the dopamine mechanism and its related genes in the hippocampus and how that may facilitate verbal communication and flexible social interaction.

Accumulating evidence of a tie between dopamine and memory suggests going one step further by making use of available data that attempt to explore the role of dopamine related genes in memory and creativity. More precisely, my hypothesis suggests that the DRD2 gene is implicated in the flexible use of language. Anatomically, DRD is expressed in the dentate gyrus and displays the functional role of mossy cells (Gangarossa et al., 2012). Due to the midbrain dopamine projection to the forebrain including the prefrontal cortex, the DRD2 gene (11 at q22-q23) has been associated with creativity and other cognitive domains (Reuter et al., 2006). Runco et al. (2011) extended the framework to include other genes as candidates for creativity, unlike the previous attempt by Runco and colleagues, which concluded that identifying candidate genes remains unclear. Their statement that "creativity will only be well understood when its genetic basis is identified" raises the thorny issue of limitations in potential approaches that might tackle the topic.

As reviewed by Shohamy and Adcock (2010), dopamine implication in memory has been probed in detail, and may be attempting to hypothesise functional parallels between memory and language, especially in the

early proposal that the uniquely human capacity to flexibly adapt to current contexts and process language rapidly in real-time situation might be enhanced by the dopaminergic system in the hippocampus. Experimental work of this hypothesis should be clarifying in comparison to other studies of creativity/flexibility in the broader sense.

Finally, from a theoretical standpoint, this chapter proposes an alternative way of investigating the neurobiological underpinnings of language by extending the brain's language network to include the subcortex. The hippocampal formation has received special attention in memory, however, how lesions in the hippocampus result in language and cognitive deficits will be discussed in upcoming chapters. Boundaries created by scholars of biolinguistics pose a major limitation, which prevents us from understanding language processing in an optimal manner. The chapter has argued several topics to strengthen the hypothesis that the hippocampus is a hub of brain network communication, not only for memory but also for language.

Although we highly benefit from animal models in understanding the complex system of the brain, I believe that hippocampal formation capacity is human specific. The salient hippocampal property that my proposal relies on is its capacity to coordinate a scattered mosaic of information across the cortex. In animal spatial navigation, reviewed findings suggest major deficits in the adaptation of spatial alterations. Likewise, in amnesic patients, findings indicate that failure in relational binding is a major impairment during verbal communication.

Issues reviewed in this chapter have been collected at various levels, including cognition and the neural connectivity of brain oscillations, in order to understand the complexity of the interconnection between the hippocampus and the neocortex, with more attention towards the PFC because it plays a pivotal role in memory storage and other executive functions. However, the assumption here is supported genetically by dopamine-related genes, namely, the DRD2 gene. It has been associated with memory and as a potential gene in creativity, and both findings are of great importance to the pursuing of a wider perspective for the basis of online language processing. In forthcoming chapters I argue the case from the perspective of neuroanatomical alteration and look at the candidate genes of several neurodegenerative diseases and syndromes, in which the hippocampus is damaged. I thereby sketch a link to language processing profiles in each chapter.

Chapter 3

Alzheimer's disease

3.1 Brian morphology and Alzheimer's disease

Alzheimer's disease (AD) is a chronic neurodegenerative brain disease that targets brain cells and results in a significant decline in cognitive functions including memory loss and language impairment (Korolev, 2014). Among neurodegenerative diseases, AD is of particular importance to neuroscientists because of its neurobiological and mental alterations. During the course of AD, from initial to advanced stages, the brain undergoes biological alterations, and these alterations may assist researchers to identify the neurobiological underpinnings of affected cognitive functions.

Due to misfolded proteins, AD patients suffer disruptions in the metabolic processes that normally maintain nerve cells in the healthy brain. AD occurs due to two prior lesions: namely, senile plaque and neurofibrillary tangle. As neurons interconnect to form a vast network throughout the brain both lesions attenuate neuron connectivity. The first of these, senile plaque contains upregulated beta amyloid protein, which causes a loss of connec-

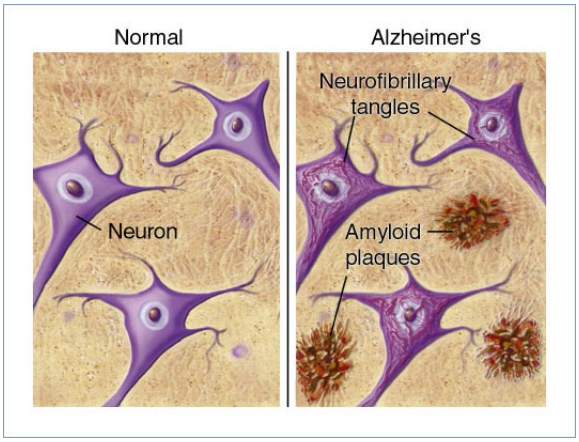


Figure 3.1: Amyloid plaques and neurofibrillary tangles in healthy and AD individuals.

tions between neurons by reacting with receptors on neighboring cells and synapses, thereby affecting their ability to function. The second neurofibrillary tangle, contains tau protein. Microtubules are an essential component of the neuron skeleton during signal travel and are highly stabilized by tau protein. In AD, however, the tau protein is defective and the result is microtubular disassociation. The accumulation of abnormal tau protein isolates one neuron from another and creates what is known as neurofibrillary tangle (Figure 3.1).

The presence of both lesions is essential in the development of AD. However, senile plaque and neurofibrillary do not follow the same pathways in the brain. For instance, senile plaque develops initially in the cortex followed by the hippocampus and other brain regions. But neurofibrillary tangle initially occurs in the hippocampus and develops throughout the neocortex. Interestingly, unlike senile plaque, neurofibrillary tangle lesion corresponds to the cognitive decline that is indicative of the potential hippocampal contribution to language and cognition, (Serrano-Pozo et al., 2011). AD patients show

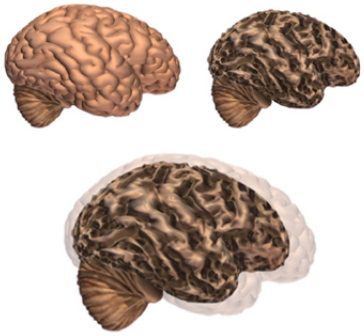


Figure 3.2: Volume of the brain in normal and AD patients.

an increase of amyloid plaques and neurofibrillary tangles causing attenuated cell connectivity that may result in cell death. Despite the fact that the onset of AD is as yet unclear, several studies showed entorhinal cortex disruption as an early physiological sign, (Juottonen et al., 1998; De Toledo-Morrell et al., 2000). Likewise, the volumetric alteration of the whole brain is a biomarker of AD (Silbert et al., 2003). See Figure 3.2. Taking into account that the hippocampal formation is one of the earliest targets of AD, it is worthwhile considering morphological variations as they occur throughout the disease and their cognitive consequences.

Despite the fact that normal ageing has an impact on brain morphology and cognition, AD is associated with a severe decline in the volume of the hippocampal formation (Figure 3.2). Nevertheless, before we tackle volumetric variations, two fundamental issues should be discussed: firstly, where decline starts and secondly how it spreads to other parts of the brain's structure.

The entorhinal cortex has been addressed as affected in the initial stages of AD pathogenesis, including altered tau protein, (Gómez-Isla et al., 1996; Du A et al., 2001; Whitwell et al., 2007; Braak and Del Tredici, 2012). MRI evidence by Pennanen et al. (2004) found that hippocampal atrophy is preceded by entorhinal atrophy, and the data revealed a 36% entorhinal cortex reduction in the AD group compared to controls and 23% to MCI subjects. The entorhinal cortex is often portrayed as a gateway that connects the hippocampus to the neocortex and the primary input resource in the hippocampal circuit. However, its major contribution to higher-order processing in the neocortex is as yet unclear. The entorhinal cortex is divided into two functional regions, the medial entorhinal cortex and the lateral entorhinal cortex. Both regions are distinguished by their microcircuitry and projections. A recent fMRI study by Khan et al. (2014), observed a relationship between AD and the lateral entorhinal cortex in preclinical disease. Data revealed that the impairment of the lateral entorhinal cortex may be implicated in short lag retention. To clarify such impairment, the entorhinal cortex in mouse models was affected when tau protein and the amyloid precursor protein were co-expressed among young mice, whereas in old mice tau protein alone gave rise to lateral entorhinal impairment.

Further, several hypotheses have attempted to identify the mechanism of AD prevalence throughout the brain, from the etorhinal cortex to the distal region effect (Meguro et al., 1999), (Khan et al., 2014) to a hierarchical pattern of revalence, which targets adjacent sites and structures connected to the entorhinal cortex. The latter hypothesis, known as transsynaptic spread, relies on the "secondary" effects of entorhinal cortex lesion in anatomically connected networks, (Liu et al., 2012). For instance,

evidence from mice detected a transformation to pathological tau from entorhinal cortex to adjacent cells and synaptically connected networks (de Calignon et al., 2012).

Pathological lesions in the entorhinal cortex tend to isolate the hippocampus from other cortical structures and are involved in volumetric changes. In comparison to healthy ageing controls, data showed a gradual hippocampal decline among AD patients. Even in AD cases that were categorized as very mild, findings indicated a greater reduction by 38% in CA1, head and lateral hippocampus compared to healthy ageing subjects (Wang et al., 2003). Generally, a reduced hippocampal volume in AD has been well reported in numerous studies. A longitudinal study by Schuff et al. (2009) observed hippocampal decline over six months and rapid decline over one year in mild cognitive impairment in MCI and AD patients, however, AD patients exhibited a higher rate of reduction.

A meta-analyses of MRI studies by Shi et al. (2009) summarized the bilateral hippocampal volume in MCI and AD, and found major bilateral lesions in both groups. However, the smaller lesions in MCI when compared to AD suggests that MCI is an initial symptom of AD. Although the extent of impairment varied in each group including controls, and results show "left-less-than-right asymmetry" across all groups.

An important lesson that can be drawn so far is that hippocampal alterations occur earlier compared to the rest of the brain, and this is of particular importance in predicting AD. Nevertheless, looking at these findings in the context of language it is likely to yield and advance the understanding of

relevant evidence in language processing.

Knowledge of the genetic bases of early and late onset of AD have been recently advanced. Thus far, the strongest genetic risk factor of AD is APOE4 on chromosome 19q13, which increases the risk of late-onset AD, modulates hippocampal alterations and accelerates the reduction of the hippocampus volume compared to normal controls (Schuff et al., 2009). Nevertheless, APOE4 negative has been associated with early onset AD and results in a rapid decline in non-memory domains, including language and attention (Smits et al., 2015). Recent findings suggest that APOE4 effects cognitive functions in healthy brains early in life, as well as navigation skills in mice, which leaves speculations on the precise early onset of the disease (DiBattista et al., 2016). Studies have focused on several chromosomes including 1, 14 and 19. Interestingly, studies of AD early-onset found a mutation in chromosome 21 across AD families. Chromosome 21, which is known as the intellectual chromosome, plays a prominent role in several cognitive and language impairments, such as Down syndrome. Since AD and DS contain various mutations in chromosome 21, DS individuals are likely to develop AD later in life. Hence, it is plausible to discuss aspects of chromosome 21 across both diseases and their implications in cognition and language, and these discussions are developed in the following chapter.

3.2 Cognitive profile in AD

Numerous studies have been devoted to memory deficits as it appears across various affected cognitive domains. Furthermore, identifying the onset of cognitive decline in AD has been vital for differing reasons. What is relevant to this proposal is the early lesion of the hippocampus and how that is manifest in parallel cognitive and language impairment.

In this section, memory and other cognitive domains are explored as they appear throughout to the course of AD. The first lesion begins in the hippocampal formation and spreads to other cortical areas that are implicated in learning, spatial navigation, attention and other executive functions. Several findings that specifically examined memory detected preclinical AD deficits. MCI is a pre-dementia stage, or a transitional phase between normal ageing and AD, and findings have indicated that there is memory deficit during this period while other cognitive domains remain intact (Grundman et al., 2004). A longitudinal study by Grober et al. (2008) found a rapid decline in episodic memory seven years prior to the diagnosis of AD, whereas other executive functions declined two to three years prior to the diagnosis.

Despite the long-standing dogma that holds the hippocampus plays a role in declarative memory, this specific function within the hippocampal formation and the medial temporal lobe (MTL) is still under debate. An interrupted neural network of episodic memory leads to major deficits in encoding and retrieval. And non-invasive evidence via fMRI has shown activation in the anterior hippocampus during associative memory tasks in healthy subjects, (Zeineh et al., 2003); (Kirwan and Stark, 2004). Interestingly, mounting evidence indicates the default mode network (DMN) participates

in memory formation, especially during recollection rather than recognition, (Kim, 2010). The DMN consists of the posterior cingulate, the precuneus and the medial prefrontal cortex, and is reported to be active during resting states. In their research into the connectivity between the hippocampus and the DMN, Sestieri et al. (2011) detected activation in the DMN parietal areas during episodic memory retrieval. Among AD patients, studies using fMRI reported decreased activation in the hippocampal formation during encoding tasks (Grön et al., 2002); (Golby et al., 2005); (Hämäläinen et al., 2007).

A general overview of the present state of empirical investment that tackles various issues in memory reveals a major concentration on behavioural and psychological processes, but It is also relevant to consider other profound issues related to the mechanism of memory encoding and the establishment of cell ensembles. Neuropsychologically, cell ensembles or engram cells enable us to formulate the memory process in certain brain structures. The memory engram or engram cell is a theory credited to Richard Semon, and refers to cell populations that maintain and retrieve memories upon external stimulus. However, research into the neural representation of memories has faced obstacles due to methodological limitations. Only recent advances in cellular and genetic biology, as well as studies in neurons and synaptic connectivity, have allowed us to observe biophysical and biochemical alterations in engram cells.

Pionner Cajal (1894) has suggested that memory storage is enhanced by strong synaptic connectivity, and this assumption led to Donald Hebb's theory of cell assembly "cells fire together, wire together" which has formed

the cornerstone of present emergence of memory and engram cells research. This kind of integration of a neurophysiology and psychology of memory has been supported by common aspects across memory and neuron synapses (Kandel, 2001).

Recently, a set of behavioural experiments identified the significant importance of engram cells in memory consolidation and retrieval. Based on previous work, further research found that mice are capable of recalling a cage where they were exposed to electrical shocks with fear, and further that this fear memory produces defensive behaviour. Pursuant to this fear caused by contextual conditioning, Roy et al. (2016), introduced anisomycin into the mice's dentate gyrus (DG) engram cells, which caused early AD. The consolidation of contextual fear conditioning demands strong in synaptic connectivity between the entorhinal cortex and the DG, which is known as long-term potentation (Nguyen and Kandel, 1996).

Disrupted engram cells that showed reduced dendritic spines similar to those found in AD cases even more suggestively resulted in a failure of the mice to recollect previous electric shocks. In a further study, Ryan et al applied optogenetic stimulations of engram cells, during which a certain ray of light activated engrams in DG that had been impaired by anisomycin injections. Mice in later experiments succeeded in memory retrieval and consequently reacted as they had to electrical shocks. These findings also demonstrated that patients do not fail in memory retrieval content due to the inflammatory processes that occur during diseases, rather they suggested a failure in the mechanism of retrieval, even while the memory remained intact.

Attention also encompasses various cognitive functions and a wide anatomical network across the brain. Thus, it is not the singular function of a certain anatomical structure, according to Posner and Petersen (1989), which plays a crucial role in the initiation of other cognitive domains such as memory, learning and language. Disregarding early memory deficits in AD, wavering attention is considered an early non-memory domain impairment, and what should be considered here is the interface between attention and the hippocampus. Given that attention and memory are cognitively linked, attention plays an important role in long-term memory encoding and recall (Hardt and Nadel, 2009), and vise versa (Stokes et al., 2012). Several studies have shown distinct neural representation and cell assemblies based on various attentional states. Evidence from studies using mice suggests that attention to the visuospatial environment in navigation enhances the stabilisation of visuospatial representation in the dorsal hippocampus (Muzzio et al., 2009). Likewise, recent findings propose that different attentional states give rise to "distinct patterns" of hippocampal activation (Aly and Turk-Browne, 2016). Observations of AD patients indicate impairment in novel tasks that require attention compared to rehearsed ones, along with early memory deficits.

3.3 Language profile in AD

Memory deficits have a strong connection to language, and individuals with AD develop a range of language impairments; for instance, verbal fluency has been well reported as a deficit characteristic of AD, Fluency is revealed

in studies in which patients are required to generate as many words as possible under certain categories (Henry et al., 2004). Although there have been intensive experimental in investigation in word finding, naming visual objects and words categorization, (Martin and Fedio, 1983; Huff et al., 1986; Price et al., 1993), language disturbance in AD seems to be more global, and the major lexical-semantic deficits named above might be preceded by other symptoms in the early stages of AD. Also, studies of the oral and written language of AD patients reveal a tendency for the patient to produce less complicated syntactic structures (Bates et al., 1995).

Several findings suggest that the individual's syntactic system remains relatively preserved in the disease's early stages, however, as AD progresses, all aspects of language deteriorate. Bickel et al. (2000) observed comprehension of various syntactic structures among AD individuals, and patients studied displayed a consistency of syntactic comprehension deficits relative to the degree of AD severity. Neuropsychologically, supportive previous findings suggest the potential role of subcomponents of the medial temporal lobe, including the hippocampus and amygdala. The morphological alterations of the "Amygdala hippocampus complex" were more correlated with verbal memory and language performance than the whole brain volume (Pantel et al., 1997). Similarly, in Bayles (2003), AD patients displayed less accuracy in language comprehension and online communication. However, early-stage AD patients did not differ from controls in sentence comprehension and assigning syntactic structure, despite the low score in their working memory (Waters and Caplan, 2002).

Less attention has been paid to the status of spontaneous language processing in AD. Given that semantic impairment and memory deficits contribute to the nature of speech, spontaneous language impairment may be an early manifestation of AD and a distinguishing parameter of AD individuals (Visch-Brink et al., 2009). Hoffmann et al. (2010) measured several temporal parameters of spontaneous speech in AD, including articulation, speech tempo and hesitation ratio. AD patients displayed significant differences in speech tempo and hesitation ratio compared to normal controls, and further, differences in articulation rate have been reported among mild, moderate and severe AD patients.

Forbes-McKay and Venneri (2005) yielded consistent results of spontaneous speech decline in AD patients during description task. This clear decline of spontaneous speech has led other studies to pursue further investigations in order to identify AD in pre-clinical stages. Through the analysis of spontaneous speech, Lopez-de Ipiña et al. (2015) identified three phases of the AD patient's speech: the phases begin with word finding deficits, followed by the lack of everyday language use, and, in the final phase, communication tends to be restricted to finite words. In this study, speech markers elicited from automatic spontaneous speech analysis observed temporal and spectral patterns, including a "nonlinear dynamic of speech", which gave an insight into detecting AD during its pre-clinical phases. Likewise, through computational techniques, Fraser et al. (2015) evaluated connected speech abnormality under specific linguistic variables, such as semantics, syntax, acoustic deficits, and information impairment. Computational analysis of previous data has detected minor heterogeneous deficits across patients with moderate and severe conditions. Based on various characteristics of spon-

taneous speech, such as length and pauses, Szatloczki et al. (2015) suggest these characteristics are more indicative of AD than other cognitive functions.

3.4 Discussion

AD is an important research area in the neurobiology of language. As cortical and subcortical structures are affected during the course of the disease, cognitive and language deficits have been shown to be early important markers. Because the nature of AD negatively influences linguistic skills, it is worthwhile examining the phases of the disease more closely and their consequences in cognition and language.

Despite available data from the research of neurobiological substrates and cognition, there is a wide gap between both fields. Research that bridges the gap between biological and cognitive alterations should provide us with a wider scope of language underpinnings. In order to understand the extent to which subcortical structures contribute to language, researchers should pay close attention to the various stages of AD and its phenotypic consequences in language and cognitive performance. By doing so we may gain a deeper understanding of, for instance, the hippocampal contribution in language.

As mentioned above, numerous studies indicate a deterioration of language aspects commensurate with the status of the disease. However, several questions remain to be addressed. Within the syntactic domain, findings

seem to be contradictory, and a heterogeneity of intact and disturbed syntactic aspects among AD patients has been reported. This kind of discrepancy in findings poses questions that are then relevant to the mounting evidence about spontaneous speech in AD. And, generally, research has found that AD individuals tend to use less complicated syntactic utterances. This tendency gives rise to the questioning of syntactic competence in AD: if syntax remains intact, why does the tendency to use simple-structured sentences appear more commonly in spontaneous speech?

Furthermore, another debate worth considering from previous studies is the neurobiological link between the course of the disease and the degree of cognition and language deterioration. For instance, a large body of evidence indicates that there is language impairment in the early stages of AD; in fact, current studies suggest using computational and automated analysis of linguistic tasks might be a pre-clinical key factor in identifying the disease. Meanwhile, early neurobiological diagnoses have detected early alterations in the entorhinal cortex and the hippocampus. This kind of early impairment should shed light on the wider brain network that underlies language processing. It underlines the role of the entorhinal cortex and its contribution to language beyond memory due to its connectivity between the hippocampus and neocortex.

Irrespective of its complexity, working memory may play a prominent role in on-line language comprehension, which requires attention and conscious information maintenance for immediate interpretations. Beyond the classical theories of the hippocampal functionality in long-term memory, recent studies have identified hippocampal recruitment during working memory

tasks (Fuentemilla et al., 2010; Poch et al., 2011). Later findings may mesh well with other evidence that attributes comprehension deficits to working memory impairment, (Kempler et al., 1998; Almor et al., 1999; Bayles, 2003). Previous evidence of hippocampal potential interaction with working memory does not omit the importance of working memory in language comprehension, but rather advocates an important hippocampal role through relational binding within certain contexts during speech.

Growing scientific effort studying the neurobiological alterations of AD provides us with strong data in favour of our proposal. This chapter aims to shed light on the importance of the hippocmpus and the extent to which it is implicated in language processing. Although we have emphasized here that language deficit in AD is related to other structures beyond cortex, the lack of medial temporal lobe (MTL) and language studies is a major limitation. In this chapter, recent literature in the field has given a general scope of severe AD language impairments, as well as describing the early symptoms of speech slowness and comprehension deficits, both of which should help to advance our understanding of the brain's language network.

Chapter 4

Down Syndrome

Down syndrome (DS) is a genetic disorder caused by an extra, i.e. third copy of chromosome 21 that occurs due to unusual cell division during fertilisation (Hattori et al., 2000). This extra chromosomal material, trisomy 21, results in intellectual impairment, including learning, memory and language. DS is characterized by unique features, which makes it an excellent model and one of the few diseases that gives us the opportunity to investigate the relationship between genes, the hippocampus and language. DS is a frequent disorder with a high prevalence rate, occurring in an average of 1 in 800 live births. Furthermore, DS patients are more likely to develop the neurocognitive phenotype profile of other diseases such as Alzheimer's disease.

Chromosome 21 constitutes 1-1.5% of the human genome and encodes approximately 255 genes, which have been identified in the 33.8 megabases of DNA of chromosome 21 (Hattori et al., 2000). Complicated genomic aneuploidy in chromosome 21 causes variable abnormal phenotypes. In recent

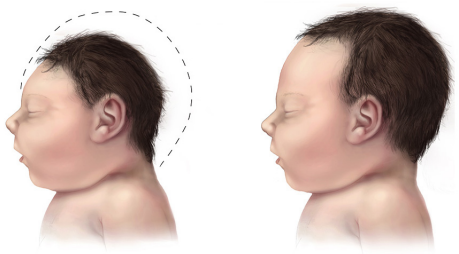


Figure 4.1: Comparison of healthy control (right) and down syndrome head formation (left).

years, studies have benefited from findings provided by advanced technological and research methods, and we have gained further understanding about trisomy 21, cellularly and neurally.

4.1 Brain morphology in Down syndrome

An important manifestation of trisomy 21 is related to brain morphology and neuron growth. Compared to healthy individuals, DS patients experience late growth with altered brain volume and configuration (Figure 4.1). Physical characteristics of DS children include microcephaly, which indicates a smaller head due to an abnormality of brain development during the embryonic phase and after birth.

The overall volume of the brain in DS is reduced (Coyle et al., 1986); (Becker et al., 1990). Likewise, MRI imaging has revealed a clearer view of various quantitative reductions in brain structures, including a small neocortex and a larger parahippocampus in DS (Weis et al., 1991); (Kesslak et al., 1994). MRI evidence in (Pinter et al., 2001b) reveals a smaller volume of

both cerebral gray and white matter, and a disproportionately smaller cerebellar volume. On the other hand, subcortical structures remain preserved. Such contradictions may be indicative of dissociation in development between cortical and subcortical structures. The latter finding was suggested by a previous study in which thalamus and basal ganglia remained intact (Jernigan et al., 1993).

The impact of trisomy 21 is predominantly on the neocortex, and involves a reduction in neural density and a smaller volume in the prefrontal and occipital lobes (Takashima et al., 1989); (Pinter et al., 2001b). Likewise MRI evidence indicates that DS individuals are at high risk of brain ageing, in which a disproportionate brain reduction occurs (Beacher et al., 2010).

Although, overall brain volume is reduced in DS (Figure 4.1), the hippocampus is selectively affected in DS (Table 4.1). Given that other adjacent structures in medial temporal lobe remain intact, this may enable us to closely examine the hippocampal cognitive functions. Several studies have reported a disproportionately small hippocampus for brain volume in DS, this reduction has not been detected in the amygdala, which seems to be the case in dementia. Unlike hippocampal reduction in AD caused by neurodegenerative alterations, hippocampal volumetric changes are due to early brain development (Raz et al., 1995); (Aylward et al., 1999); (Pinter et al., 2001a).

Having looked at morphological alterations, we move forward to the hippocampal neural circuits, which seem to be affected in DS. Indeed the re-

Brain region	Newborns	Adults (20–50 years of age)*	Elderly individuals (>50 years of age)*
Whole brain	Almost normal weight	Reduction in weight, brachycephalic	Smaller overall cerebral volumes
Prefrontal cortex	Reduction in volume	Reduction in volume	Reduction in volume
Parietal cortex	Normal or reduction in volume	Reduction in volume	Unknown
Temporal cortex	Narrow superior temporal gyrus	Reduction in volume of right middle or superior temporal gyrus	Decreased grey matter volume in posterior cingulate and entorhinal cortex
Hippocampus	Unknown	Reduction in volume	Unknown
Parahippocampal region	Unknown	Increase in size of the parahippocampal gyrus	Reduction in volume
Amygdala	Reduction in volume	Reduction in volume	Reduction in volume
Cerebellum	Reduction in volume	Reduction in volume	Reduction in volume
Brain stem	Reduction in volume	Increase in grey matter volume	Degeneration of locus coeruleus
Basal prosencephalon	Almost normal size	Normal	Degeneration of basal prosencephalon cholinergic nuclei (nucleus of Meynert)

Table 4.1: Brain alteration in various brain structures in Down syndrome throughout life. Adapted from (Dierssen, 2012).

duction of volume is followed by reduction at the synaptic level and in the ramification of dendritic trees. However, the neural network of DS and how it contributes to cognitive and language deficits is still unknown. It is believed that mental retardation and cognitive deficits in DS are results of cortical synaptic dysgenesis (Becker, 1991). Within the hippocampal circuits, pyramidal cell abnormalities give rise to cognitive impairments related to learning and memory. Developed models of triplicated chromosome 21 mice have advanced our understanding of neural circuit mechanism.

Electron-microscopic hippocampal findings from Ts65Dn mice in (Kurt et al., 2004) indicate significant reduction in neuron density and synapses in certain subregions in the hippocampus, When compared to diploid mice, Ts65Dn mice exhibit significantly lower neuron density in CA1, whereas, synaptic densities and synapse-to-neuron ratios were significantly reduced in the DG, CA3 and CA1. Detected synaptic abnormality in this study sug-

gests an associative deficits in either axon terminal formation or development of dendritic arborization. In part, dendritic arborization is affected by reduced cortical postsynapses, which may give rise to reduction in synaptic density. (Suetsugu and Mehraein, 1980) quantitatively observed the spines in the cingulate cortex and the hippocampus in seven DS patients, and the quantity of spine in the middle and distal segments of the apical dendrites was significantly fewer compared to normal subjects. Interestingly, a third group of unspecified mental retardation did not exhibit any decrease compared with normal subjects. Likewise, the dendratic spines of CA1 and CA3 pyramidal neurons were significantly reduced in two cases of DS compared to healthy controls (Ferrer and Gullotta, 1990).

Recently, special attention has been paid to CA3 due to its multiple resources of input, including mossy fiber inputs from the dentate gyrus (DG) and entorhinal cortex (Amaral, 1995). Hanson et al. (2007) investigated CA3 synaptic connectivity in Ts65Dn mice, and results show specific synaptic alterations in CA3- increased associational connections in the subregion while excitatory and inhibitory input were decreased, which may indicate a dysfunction in presynaptic populations in CA3. These important changes have been supported by evidence of rearrangement of presynaptic complexes local connectivity throughout life where experience and age play major roles in learning and memory (Galimberti et al., 2006). An intriguing finding revealed that DG-CA3 is particularly important in the neural and cognitive network in DS. In transchromosomic Tc1 mice of DS model (Galimberti et al., 2006) identified a dysfunctional connectivity in the DG-CA3 network that may potentially be involved in the intellectual deficits that occur in DS.

4.2 DYRK1A

Among 33 genes in the DS critical region, DYRK1A (dual-specificity tyrosine phosphorylation-regulated kinase 1A) has been investigated as a candidate gene that underlies morphological alteration and cognitive impairment (Park and Chung, 2013). Clinically, DS patients are more likely to develop Alzheimer's disease (AD) later in life (Lott and Head, 2001); (Menéndez, 2005). (Møller et al., 2008) and (Courcet et al., 2012) studies DYRK1A overexpression in relation to microcephaly, brain growth and cognitive deficits in DS. (Dowjat et al., 2007) studied DYRK1A overexpression not only in early brain development but also during adulthood. However, the development of AD encouraged several investigations to research DYRK1A, a common gene that may contribute to both illnesses. Interestingly, DYRK1A has been detected to be abnormally expressed in AD (Ferrer et al., 2005). DYRK1A overexpression implicates in neural loss and early onset of neurodegenerative disease due to tau and amyloid precursor hyperphosphorylation among DS individuals (Park et al., 2007); (Liu et al., 2008) (Figure 4.2). Previous evidence from Yang et al. (2001) showed a strong correlation between DYRK1A and hippocampal neural differentiation, including reduction in hippocampal dendritic spine formation (Park et al., 2012). Likewise, data reveal neurogenesis and cognitive alterations in the DG due to DYRK1A overdose (Pons-Espinal et al., 2013).

DYRK1A seems to be a crucial gene that contributes to a wide range of DS physical and intellectual phenotypes as well as other neurodegenerative diseases. What is relevant to our proposal is the common hippocampal alterations caused by DYRK1A, which occur in both DS and AD and their

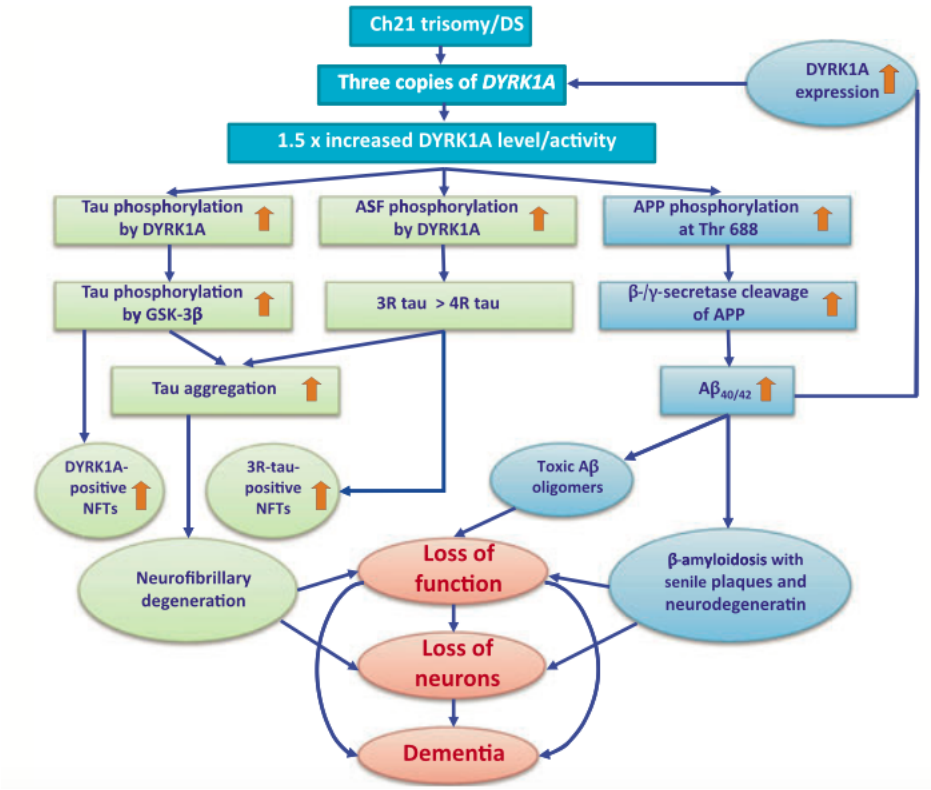


Figure 4.2: Schema of DYRK1A overexpression contribution to B-amyloidosis and neurofibrillary degeneration in DS. As indicated overexpressed DYRK1A results to two pathways of neurofibrillary degeneration and one contributing to brain -amyloidosis. From (Wegiel et al., 2011).

cognitive consequences.

Such a wide implication of DYRK1A along with various substrates in DS encouraged other studies to suggest two related issues, namely, its effect on the brain and skull in modern humans. The hypothesis of the human language-ready brain posits that brain growth gave rise to the modern human skull and its globular braincase configuration, which enables us to process language and execute sophisticated cognitive tasks (Boeckx and Benítez-Burraco, 2014b); (Boeckx and Benítez-Burraco, 2014a); (Benítez-Burraco and Boeckx, 2015); (Boeckx, 2016). This promising enterprise combines with previous compelling evidence from DS research, which indicates skull malformation and altered brain growth among DS patients. DYRK1A is a candidate gene that is likely to yield on its own an important comprehension of brain and language and may resolve one of the remaining questions about the relationship between language, neurogenesis, brain growth and the configuration of modern humans, saying as outlined above, that brain development might be induced by the neurogenesis of the DG.

4.3 RCAN1

Another gene worth considering is RCAN1, which is located within the DS critical region and consists of seven exons (Fuentes et al., 1997). An excess of RCAN1 expression results in a DS phenotype, in fact both DYRK1A and RCAN1 act cooperatively in DS. RCAN1 inhibits the protein phosphatase calcineurin, which interacts with the clacineurin pathway (Fuentes et al.,

2000); (Rothermel et al., 2000). As a regulator of calcineurin, RCAN1 is highly overexpressed in the cortex and the hippocampus (Hoeffer et al., 2007); (Mitchell et al., 2007), and in other substructures involved in learning and memory, including the basal ganglia (Ermak et al., 2001); (Montoya et al., 2014).

A mice model of DS, which received an increased dosage of Rcan1, showed an impaired development of the sympathetic nervous system. Whether Rcan1 is the primary cause, Patel et al. (2015) concluded that Rcan1 alone is capable of attenuating neurons and decreasing innervation in the mice model. Among the complexity of genetic disorders including DS, two key genes, DYRK1 and RCAN1, contribute at various levels, neuropathologiacally and cognitively. Understanding the molecular mechanism of neuropathological properties can offer us a suitable tool to delineate the neurobiological underpinnings of the development of language and cognition in DS.

4.4 Cognitive profile in DS

Any attempt to understand how neurobiology underlies certain cognitive aspects requires a clear vision of abnormal development on several levels, including the genome, connectome and dynome. In fact, DS is one of the diseases that has drawn major attention within a single discipline. Recently, a few attempts at more comprehensive examination have outlined an important correspondence.

Determining the DS cognitive profile is relatively challenging due to genetic variations and development during ageing, which need to be taken into consideration (Zigman and Lott, 2007). Nonetheless, there are several phenotypes which apply to DS in general. Cognitive delay is a major impairment in DS. Associated with cognitive delay, weak integration of visual and spatial information in learning is often present among DS individuals. DS Ts65Dn mice models exhibit a lack of skill in complex learning tasks (Reeves et al., 1995).

Central to DS learning issues is that the DS individual's working memory capacity is lower than that of healthy individuals. Working memory is known for its storage function, information flexibility and manipulation in learning and everyday cognitive processes. Working memory plays a prominent role not only in learning but also in language processing. Substantial evidence has shown a lack of short verbal memory capacity in DS (Broadley et al., 1995); (Jarrold et al., 1999); (Gathercole and Alloway, 2006). An overview of empirical working memory literature in DS indicates that a large body of results have been driven by a range of verbal and linguistic experiments, which may fit in the following section about language profiles in DS. Contrary to previous findings, long-term memory and synaptic plasticity are preserved despite spatial working memory disturbance (Morice et al., 2008).

The mental retardation characteristic of DS is accompanied by motor skill abnormalities and a major delay in motor skills during the development period, which includes fine and gross motor skills (Connolly and Michael, 1986). However, it has been suggested that there is a grater delay relative to motor complexity (Pereira et al., 2013).

4.5 Language profile in DS

Language is another domain that is largely impaired in DS. Based on various findings and studies, language in DS individuals has been well investigated among other neurodegenerative diseases (Chapman and Abbeduto, 2003); (Clibbens, 2001). During the development of language DS children experience speech delay early in life, likewise their vocabulary growth is delayed, which results in the construction of shorter constructions of phrases compared to normal subjects (Bray and Woolnough, 1988).

From a theoretical standpoint, language impairment in DS is attributed to morphological alterations in physical appearance and brain dysfunctions, which result in cognitive and mental retardation. Hence, it is appropriate to briefly summarize each deficit individually.

4.5.1 Oral motor development

Morphological abnormalities in the skull and craniofacial extend to speech production structures. Tonal processing in DS individuals is distinctive from normal individuals due to biological differences that affect oral and motor development, such as enlarged tonsils and adenoids, and a high and narrow arched palate. Further, the jaw and mouth are small relative to the size of the tongue Strome and Strome (1992); Miller and Leddy (1998); Uong et al. (2001). See (Figure 4.3).

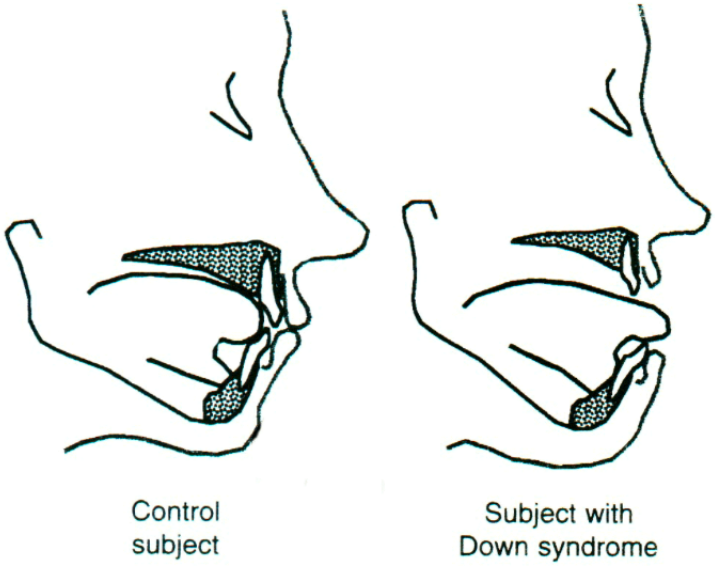


Figure 4.3: comparison of the state of oral structures at rest in DS individuals and healthy controls.

In addition to the mentioned oral characteristics, weak muscle tone negatively influences intelligibility of speech and impedes patients from appropriate sound production, as has been observed in the communication phenotype of the fragile X syndrome and DS (Barnes et al., 2006). Likewise, vulnerable musculature gives rise to major slowness, discoordinated speech and inconsistent pronunciation, (Dodd and Thompson, 2001). However, several studies of early development failed to report remarkable differences in speech-like vocalization in comparison with typically developed infants (Smith and Oller, 1981); (Steffens et al., 1992). In contrast, other observations indicate a higher number of nonspeech sounds among DS infants (Legerstee et al., 1992) and a general delay of canonical babbling onset compared to ordinary infants (Lynch et al., 1995).

Within this specific domain of speech production, a large body of evidence attributes deficits to craniofacial morphology and vocal system ab-

normality rather than language constructions and cognition (Kent and Vorperian, 2013).

4.5.2 Semantics

Semantic knowledge of DS is often discussed within the context of vocabulary development, social interaction and cognition. However, it is plausible to tackle this issue through a certain frame, taking into account the strong implication of declarative memory and the hippocampus in semantic knowledge and social interaction. Based on the main proposal of the thesis, we argue that there is a significant hippocampal contribution at different phases, which effects the early development of vocabulary, social interaction knowledge and the pragmatic use of language.

Unlike typically developing children, DS children exhibit a major delay in early vocabulary development (Berglund et al., 2001), followed by slow progress (Yoder et al., 2004). This delay in vocabulary development is not isolated from the general cognitive delay in DS, as has been stated in the cognitive profile section. Likewise, an expressive language delay may develop later in life. In comparison to specific language impairment Laws and Bishop (2003) found expressive language effected not only in children but also among DS adolescents.

Pragmatic language and using language in social interaction requires contextual attention and a capacity for retrievability of previous discourse in coordination with linguistic output. Despite an inconsistency in findings,

aspects of social interaction remain to be further investigated. In a non-face-to-face interaction, adults with DS show serious deficit in their ability to maintain interaction and produce incoherent discourse (Abbeduto et al., 2006). An interpretation of lagged interaction is that it might be due to a shortage of hippocampal implication and the general delay of cognitive functions in DS. Linguistic interaction abnormality in DS is a continuation of a prelinguistic intentional communication, such as eye gazing and gestures (Abbeduto et al., 2007), which may later lead to an adaptation of a specific communication strategy that lacks flexibility and creativity in social interaction.

Given that DS individuals exhibit strengths and weaknesses in various aspects of speech interaction, a clear vision of an interaction profile remains to be supported. Although social behaviour in DS individuals remains intact, cognitive impairment plays a role in shaping online language processing.

4.5.3 Syntax

Along with word meaning, language requires a specific arrangement of elements in order to construct a sentence. Syntax comprehension/production in DS is challenging. In syntactic comprehension tasks, findings from Miolo et al. (2005) indicate late comprehension due to semantic and syntactic weaknesses. Other supporting evidence suggests that speech processing is associated with grammatical deficit. In processing contrasting syllables, event-related potentials display smaller amplitude differences among DS children with greater impairment in grammatical morpheme comprehension (Yoder et al., 2006). In language production, DS patients display deficits in syntactic aspects of speech, which coincide with other cognitive domains. DS

children develop difficulties in communication and a general delay in the transition phase from one- to two-word speech (Iverson et al., 2003). A recent longitudinal study that took place over the course of one year examined narrative development in DS children, aged 5-16 years, in which results would indicate the development in semantic complexity; however, syntactic complexity did not exhibit such improvement (Mosse and Jarrold, 2011).

Grammatical morphology deficits in DS have been further investigated in studies by Chapman (1997); Rondal and Comblain (1996). In comparison to specific language impairment and typically developing children, individuals with DS exhibited a delay in grammatical morphology production across various measurements (Yoder et al., 2006). Language profiles improve as DS individuals advance in age, and during adulthood progress in language production and complex syntactic processing was observed (Thordardottir et al., 2002). One interpretation of this progression in syntax suggests that the late growth of neural network and its plasticity may enhance higher complexity of syntactic structures.

Despite the wealth of studies in DS language and communication, one can note less illustration in the interconnectivity of cognitive/behavioural phenotypes, such as attention, flexibility, working memory, social behaviour and language deficits. Likewise significant implications at the neurobiological level remain to be identified. Another issue is that major studies have been devoted to the question of "what" rather than "how", and various studies of aspects of language impairment have reported that such a mechanism remains unknown, especially in how the genome and connectome contribute to these deficits.

4.6 Discussion

In this chapter we outlined cognitive and language deficits in DS as well as the neurobiological abnormalities that give rise to DS phenotypes. Indeed the field of DS is complicated due to various factors, such as brain growth, skull/craniofacial morphology, neurobiological connectivity and the wide interaction of genes. Relative to the proposal here is the hippocampal contribution to different facets of cognition and language. To refine current assumptions one needs to integrate cognitive and behavioural findings with recent genetic and neurobiological results, which we attempt to achieve with close attention to the hippocampal-PFC connectivity.

The literature of DS indicates that delay is a common feature in cognitive and language performance. Likewise, in the brain level, a weak communication exists between brain regions due to the delay in neural system development. An early theory by Nadel (1999) associates "late-developing" neural underpinnings to the DS cognitive profile, which includes the prefrontal cortex (PFC), medial temporal lobe (MTL) and the cerebellum. Previous hypotheses are worth consideration, given that poor connectivity of various brain regions can be detected as parallel with behavioural performance. To enhance our understanding of neurobiological implications, some aspects of late development of neural system are discussed.

Altered neural development appears during the prenatal/postnatal period, and this has a direct impact on neurogenesis, myelination, neural abnormality in the granular layers and brain maturation. In a study that included DS children from birth to 5 years old, Wisniewski (1990) reported similarity in newborn DS infants' brain shape to healthy controls, however, abnormality

of maturation and myelination delay are reported after 3-5 months of age. Myelination plays a central role in learning and cognition (McKenzie et al., 2014); (Huang et al., 2009). In a study of the sequence of myelination in the human hippocampal formation in DS and healthy controls, Ábrahám et al. (2012) showed that DS patients have a sequence of myelination of the hippocampus that follows a similar developmental pattern to that in controls; nevertheless, DS showed a general delay in myelination with decreases in myelination in the DG from early age until adulthood. Reported delay and decreased density of myelination attenuates hippocampal circuits and connectivity to the PFC and adjacent structures. Other MRI findings associate cognitive dysfunctions with a reduced right hippocampus, whereas other subcortical structures such as basal ganglia, remain intact (Aylward et al., 1997).

Although DS individuals have smaller brains compared to typically developing individuals, MTL display the progressive decrease with ageing associated with AD cognitive profile (Teipel et al., 2004). Longitudinal observations of cognitive functions and IQ scores coincide with previous evidence of delayed development of neural system. In Carr (1988), children with DS showed a sharp decrease in IQ scores: they achieve a score of 50 at the age of 4 years, whereas they achieved a score of 70 at 6 months of age. In a task that requires hippocampal activation, Mangan (1992) found that spatial learning in DS children is impaired compared to controls. In contrast, in another hippocampal-independent task (response-based tasks) DS childrens performance matched that of the control group. Likewise, preschool DS children have shown spared capacity to retrieve spatial positions in sequence Edgin et al. (2010), which suggests that their spatial memory is

relatively intact compared to other memory tasks that demand a high level of relational binding and flexibility.

In parallel with the hippocampal deficits, the PFC is reported to develop abnormally during early adulthood. The PFC is known for executive function and high cognitive processing (Miyake et al., 2000). DS altered developed PFC is highly involved in various cognitive deficits that have been discussed in the cognitive profile section, including working memory and lack of flexibility during spatial tasks. Generally, findings that show greater impairment of DS adults compared to children reinforce the significant role played by the MTL, including the hippocampus which undergoes alteration during adulthood.

In the case of DS, the neurocognitive phenotype should follow a general approach of globularity with special attention to communication patterns between brain regions. Rather than examining individual structures, this approach should not, however, omit the importance of certain structures. For instance, in our proposal, hippocampal-PFC connectivity plays a prominent role because it contributes to learning, memory and various cognitive tasks that require high level of flexibility (Winocur and Moscovitch, 1990); (Yoon et al., 2008); (Preston and Eichenbaum, 2013); (Jin and Maren, 2015); (Malá et al., 2015). In contrast, hippocampal-PFC weak interaction is associated with poor verbal and spatial performance (Pennington et al., 2003).

Unlike in other syndromes, the language profile in DS has been examined more than other cognitive domains. In fact, one of the limitations of DS cognitive observations is an over-replication of linguistic and verbal mem-

ory tasks, which reveal results that can be under debate. Further, language studies in DS individuals lack an examination of neurobiological mechanisms, which may contribute to the field of neurobiological foundations of language.

Broadly speaking, DS brain development appears to be normal at birth, and abnormality increases during childhood and adulthood. Although the brain is initially microcephalic, greater volume reduction is later observed in the hippocampus, PFC and cerebellum more than in other brain structures, which may hold implications for language deficits. Indeed, further investigation is needed to enhance current hypotheses of subcortical implications in language and cognition.

Chapter 5

Williams' Syndrome

5.1 Introduction

Williams' syndrome (WS) is a rare genetic condition that occurs in 1/7,500 births, and is due to the deletion of 28 genes on chromosome 7q11.23 (Peoples et al., 2000; Scherer and Green, 2004; Morris, 2010). WS patients are characterized by intellectual disability, developmental delay, language difficulties in early childhood, cardiovascular diseases, dysmorphic facial features, and hyperactive social interaction. This chapter follows the DS chapter because it is in part related to cognitive phenotypes, and there are several contradictory aspects that will be tackled in the discussion section.

Chromosome 7 is known to be relevant to other syndromes that are characterized by abnormal microcephaly, facial malformation, and cognitive disability, such as Shwachman-diamond syndrome (Scherer and Green, 2004). Also, RussellSilver syndrome, (Nakabayashi et al., 2002) is linked to both chromosomes 7 and 11. Further, the gene FOXP2, is located in 7q31, which has been associated with language and speech disorders is located in 7q31

(Lai et al., 2001).

5.2 Brain morphology in Williams' syndrome

WS research is another opportunity for various interdisciplinary studies attempt to make connections between genetics, neuroanatomy, and cognition factors and conditions. Although, WS has been less invistigated than DS, current literature about the condition helps to sketch potential correlation among previous disciplines. Reviews of the morphology and gross anatomy of the WS brain it aim to link alterations at the neuroanatomial level to candidate genes and the behavioural concequences. A major diagnostic feature of WS is craniofacial dysmorphology, including a short anterior cranial base, a steep angle of the mandibular plane, and a deficient chin button (Mass and Belostoky, 1993). A cleft palate has been reported in some cases (Blanco-Dávila and Olveda-Rodriguez, 2001). A comparative illustration of these features is provided in Figure 5.1. In a detailed study, Axelsson (2004) found that the WS neurocranium is generally distinctive from typically developing individuals in shape and volume. The overall alteration consists of a flattening of the superior parietal bone and large posterior occipital bone, which fit in concert with brain malformation.

At the brain level, several alterations have been documented. Findings derived from MRIs have identified the abnormal development of several neuroanatomical structures. Unlike DS, the brain of WS individuals brain tends to be decreased in posterior width and extended in the posterior to anterior

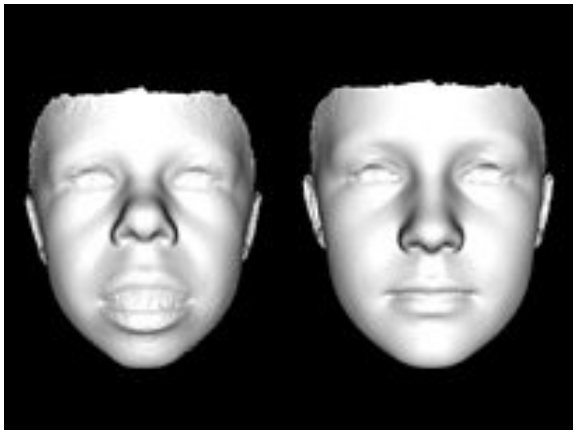


Figure 5.1: comparison of WS craniofacial (left) to typically developing features (right).

length (Bellugi et al., 1990). An overall reduction in the cerebrum of WS patients was found in several studies (Reiss et al., 2000; Sampaio et al., 2008; Osório et al., 2014).

Inspections of WS brain patterns in the research by Reiss et al. (2000) have indicated normal cerebellar volume, whereas the brain stem appeared to be relatively decreased. Abnormal patterns of the posterior fossa might be indicative of certain characteristics of WS central nervous system (CNS). Although, the brain's grey matter maintains its formation, later research suggests that CNS abnormality may give rise to reduced white matter.

Two main characteristics of the WS brain have been documented: a significant reduction in the surface area and combined increased cortical thickness and cortical complexity (Fahim et al., 2012; Meda et al., 2012). Less attention has been paid to the subcortex in WS, however, some structures have been more investigated. For instance, WS shows a curtailed activation of the amygdala, and abnormality in the orbitofrontal-amygdala circuit

are involved in non-social anxiety, (Meyer-Lindenberg et al., 2005a). Similarly, research has reported the WS basal ganglia to be disproportionally decreased in volume (Chiang et al., 2007).

Unlike DS, where the hippocampus is impaired in various aspects including morphology and circuits, hippocampal formation in WS exhibits functional abnormality, whereas the volume remains statistically comparable to healthy individuals, (Meyer-Lindenberg et al., 2005b), see in Table 5.1 below.

Hippocampal size

	Left hippocampus (mm^3)	Right hippocampus (mm^3)
WS	3259.9 ± 110.8	3349.3 ± 137.1
Controls	3300.4 ± 114.9	3452.0 ± 142.3

Table 5.1: Comparable measurement of hippocampal volumes between WS and healthy individuals. Adapted from (Meyer-Lindenberg et al., 2005b).

In contrast, other studies have reported reduced volume of the hippocampus and a reduced surface of the parahippocampal gyrus, (Meyer-Lindenberg et al., 2005a; Meda et al., 2012), as shown in Figure 5.2.

WS hippocampal dysfunction is correlated with reduced regularity of N-acetyl aspartate (NAA) (Baslow, 2003). NAA is an amino acid, which is mainly concentrated in the neurons of the adult CNS, and is strongly related to high-energy phosphate metabolism in the hippocampus (Pan and Takahashi, 2005). Meyer-Lindenberg et al. (2005b) have reported decreases in the NAA in the left hippocampus of WS subjects, which may lead to irregular consequences of long-term potentiation. Regardless of volume preservations, previous study indicates abnormal activation and decreased blood

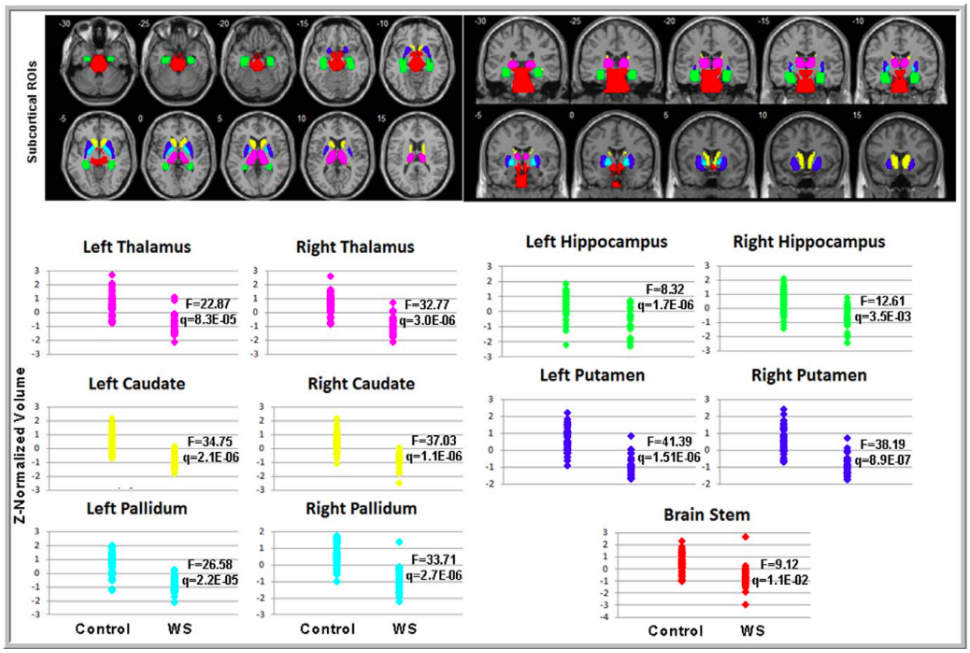


Figure 5.2: (Top) coloured anatomical structures indicate differences in volumes, (bottom) among several subcortical regions,green plots show (Z-normalized) decrease in hippocampal volume in WS individuals compared to typically developed ones. From (Meda et al., 2012).

flow in the hippocampus. Hippocampal function is, therefore, impaired in long-term memory and spatial navigation. While spatial navigation involves the parahippocampus in addition to the hippocampus (Burgess et al., 2002; Epstein, 2008), a projection between the hippocampus and the parahippocampus may be attenuated in WS, and it is plausible that the parahippocampus contributes to some extent to abnormal hippocampal functions to some extent.

The literature of WS suggests significant weakness in the visuospatial realm, and observations of neural mechanism reveal hypoactivation of the dorsal "where" pathway in the parietal region (Meyer-Lindenberg et al., 2004). Such functional abnormality of the dorsal stream may give rise to input shortage in the parahippocampus.

5.2.1 LIMK1

At the genetic level, the deletion of 26-28 genes on the long arm of chromosome 7 that is found in WS provides us with several opportunities. Firstly, to understand the roles of certain genes in cognition and behaviour, and, secondly, to advance our understand in the field of language and cognition through a comparison of the available data of the cognitive and linguistic performance in WS and DS, as it is appears between genotype and phenotype. Among deleted genes, three genes -LIMK1, CYLN2 and FZD9- have been examined in relation to behaviour and cognition (Figure 5.3).

LIMK1 regulates actin filament dynamics via the inhibition of ADF/cofilins. Actin filament is a major component of the neural cytoskeleton that participates in neurodevelopment and neuron migration and localization through-

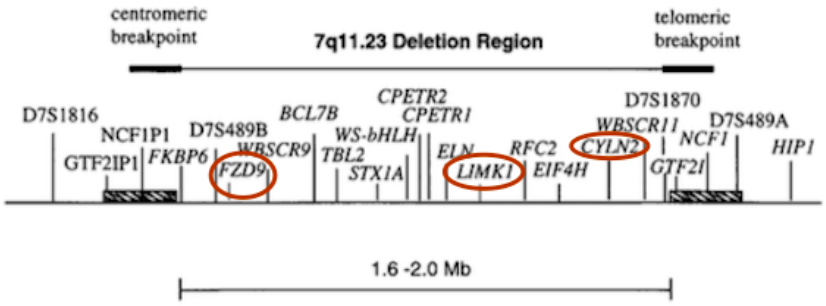


Figure 5.3: Map of genes in WS deletion region including LIMK1, CYLN2 and FZD9. (Francke, 1999).

out the brain. LIMK1 is highly expressed in the regular development of the central nervous system (Scott and Olson, 2007). The prominent role of LIMK1 in the CNS corresponds to synaptic and dendritic spine growth. For instance, deletion of LIMK1 in mice models has established an atypical development of spine and synapses due to the irregularity of the actin cytoskeleton. In neuron maturation, actin is essential to formulate synapses (Sheng and Hoogenraad, 2007). It is likewise involved in spine development and connecting dynamics (Hotulainen and Hoogenraad, 2010), and cell migration (Scott and Olson, 2007).

Within the hippocampus, the dynamics of dendritic spines are essential for synapse connectivity, which plays a major role in spatial navigation and memory. Mice models with LIMK1 knockout reveal notable alterations and abnormalities at physiological and behavioural levels. Intriguing findings by Meng et al. (2002) observed significant alterations in spine morphology and synaptic function that were ascribed to a significant curtailment in cofilin phosphorylation. The study's findings revealed that dendritic spines are relatively reduced in the head and thicker neck region compared to LIMK1

+/+ mice (Figure 5.4), which results in a shortage of density in hippocampal postsynaptic receptors.

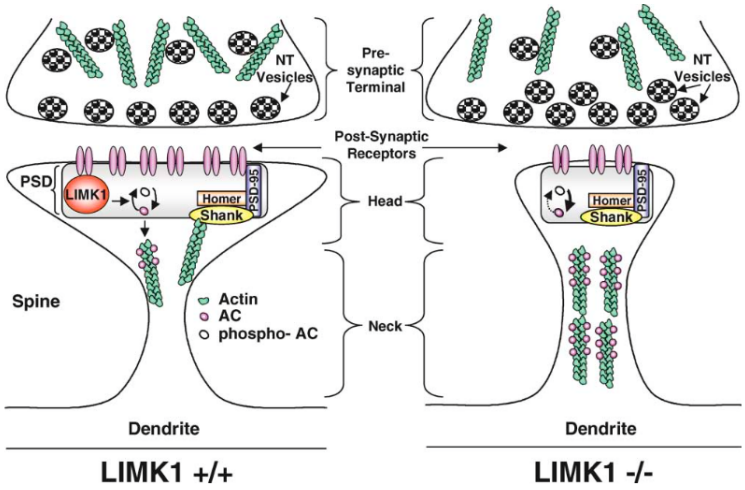


Figure 5.4: Illustration indicates the implication of LIMK1 knockout mice compared to typical model. Dendritic spine consists of neck, head and postsynaptic density. Morphological changes are present in LIMK1-/- as addressed in Meng et al. (2002), including a thick neck and decreased postsynaptic density, which may disrupt long term potentiation.

5.2.2 CYLN2

Cytoplasmic linker 2 (CYLN2) is related to the linkage between microtubules to the dendritic lamellar body (De Zeeuw et al., 1997). Although the role of CYLN2 is not well understood, recent studies have provided new insights in their attempts to associate CYLN2 to certain characteristics in WS, where CYLN1 has been found highly expressed in the cerebellum and subcortical structures, namely the hippocampus and the amygdala. In a CYLN2-knockout mice model compared to wild type, Hoogenraad et al. (2002) found overall results that resembled WS phenotypes. Deleted CYLN2 mice exhibit

slight deficit and abnormality in brain growth during the postnatal period, less motor coordination, and hippocampal dysfunction. Unlike other studies, Hoogenraad and colleagues did not detect smaller brain volumes, however, the corpus callosum was found to be smaller than in the wild type group.

Van Hagen et al. (2007) also investigated implications of CYLN2 and GTF2IRD1 via various cognitive and motoric tasks. The study reported the case of a patient in which STX1A and LIMK1 were deleted, whereas CYLN2 and GTF2IRD1 remained intact. The study also recorded the performance of GTF2IRD1-CYLN2 knockout mice. Findings demonstrated that the patient performed better compared to typical WS individuals, even though gene deletion occurred partially in the reported case. Nevertheless, CYLN2 mutant mice provided confirmation of previous results, in which the morphology of the corpus callosum seemed to be smaller than normal and disturbed behavioural tasks were reported. Together the findings from the patient and mice studies indicated a significant role of CYLN2 in the WS hippocampus and cerebellum and their assigned cognitive capacities.

5.2.3 FZD9

Frizzled class receptor 9 (FZD9) was previously called FZD3. FZD9 lies in the region of chromosome 7q11.23 deletions in WS. The FZD9 gene is predominantly expressed in the brain, skeletal muscle, and other organs. Recent evidence has suggested that FZD9 plays a vital role in hippocampal development. Although FZD9-deleted mice exhibit a regular gross anatomy of the hippocampus, results from studies have reported an increase in apoptotic cell death -the process of destroying no longer needed cells- in the DG. Cognitively, mice studies also showed severe deficits in visuospatial learning

and memory (Zhao et al., 2005).

5.3 Cognitive profile in WS

Cognition in WS seems to be heterogeneous with WS individuals exhibiting strengths and weaknesses in various cognitive domains. Despite an uneven profile, studies label WS as a specific category of language and cognition. Generally, findings have revealed that WS patients perform normally in language and face recognition (Rossen et al., 1996), however, they have major deficits in visuospatial abilities, learning, and memory tasks.

Social cognition in WS has been well documented among other cognitive domains. Despite their intellectual limitations, individuals with WS display striking social engagement, which is also associated with strong expressive language (Jones et al., 2000). Given that a set of genes on 7q11.23 has been identified as the region critical to WS, consistent salient characteristics of the WS social profile are key factors in uncovering its neurogenetic underpinnings, especially in light of recent advances in neurobiological techniques across disciplines. At the level of phenotype, an early emergence of hypersociality has been observed in children aged 15 to 58 months. Regardless of the general delay in other cognitive domains that WS patients experience, Jones et al. (1998a) reported an early independent hypersocial profile. Children with WS display highly expressive and social interaction compared to their matching controls. Likewise, WS children show uncontrolled behaviour when approaching and communicating with strangers. Such fearless inter-

action is enhanced by their clear expressive language (Gosch and Pankau, 1994; Doyle et al., 2004). Facial processing is essential in order to form appropriate social behaviour, and initial evidence indicates that WS patients are preserved in face processing, and spend more time looking at faces, and are able to recognize them in various circumstances (Jones et al., 1998b; Bellugi et al., 2000).

Several studies have attempted to link the WS social profile to an atypical development of the brain. A general assumption assigns WS social aspects to the large volume of their amygdala (Reiss et al., 2004; Martens et al., 2009). The amygdala is a major component of the limbic system with a direct projection to the hippocampus and connections to other brain regions related to sensory system, emotions, memory, and facial processing (Fried et al., 1997; Jawaid et al., 2008). In a study devoted to the link between hypersociability and the amygdala, Martens et al. (2009) sketched a relationship between the volume of amygdala in WS and their hypersociable aspects. Findings detected that the disproportionate increase gives rise to a higher approachability in the assessment of negative and positive faces compared to control subjects. Previous evidence, however, leads us to examine the related visuospatial domain, including construction and navigation, where WS patients exhibit major deficits. For instance, the strategy of encoding in people with WS relies heavily on landmarks in spatial learning and way finding, and fails to learn navigation in a landmark-free route (Broadbent et al., 2015). Likewise, WS individuals demonstrate weakness in visuospatial construction (Nakamura et al., 2001; Mervis and Klein-Tasman, 2000).

Previous findings seems to be contradictory in that, while WS individuals demonstrate remarkable strength in face processing, they also exhibit severe weakness in spatial construction. The fact that both face processing and spatial navigation fall under the category of visuospatial cognition, this dissociation within visual processing raises the question of whether neurobiological bases abnormality has occurred. The visual system has been associated with two different hierarchically arranged neural systems in the brain, namely the dorsal and ventral pathways. This classification of pathways, or streams, is credited to Ungerleider (1982), who discovered there is a division of labor between the two streams. The dorsal, or "where" stream, is linked to spatial cognition, and the ventral, or "what" stream, to object recognition. A wealth of evidence shows that WS-impaired spatial processing is due to an insult in the dorsal stream, whereas the ventral stream remains intact, which may give contribute to patients outstanding performance in face processing (Atkinson et al., 1997; Paul et al., 2002), as illustrated in Figure 5.5.

Nevertheless, deficits in spatial navigation are due in part to the hippocampal abnormality in WS. In mice studies frizzled 9 knockout, which is one of deleted genes in WS, results in atypical development and cell death in the hippocampus, and mutant mice demonstrate severe defecits in visuospatial learning and memory (Zhao et al., 2005). Other executive functions in WS, however, have been less examined. Few studies have investigated higher cognitive processes, such as attention, inhibition, planning, set shifting, cognitive flexibility and planning. In a study that examined inhibition and frontoparietal circuits, WS children aged 4-15 showed better results in verbal inhibition than the control group, whereas their spatial inhibition

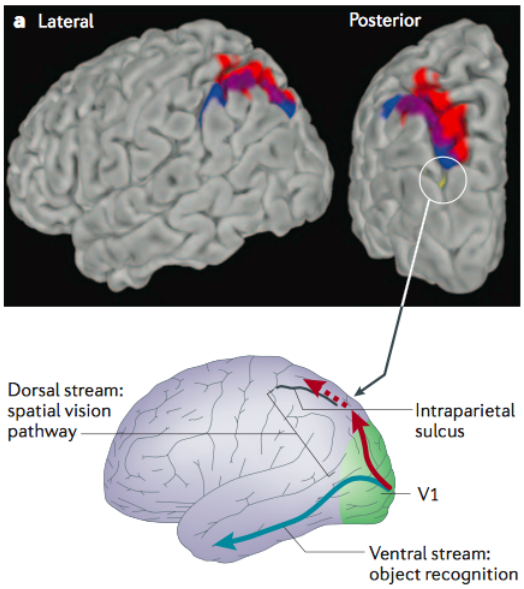


Figure 5.5: An illustration indicating both ventral and dorsal pathways with a consistent functional impairment in the dorsal visual stream adapted from (Meyer-Lindenberg et al., 2006).

performance was lower (Atkinson et al., 2003). Although studies claim that inhibition is the primary impairment in the frontal cortex (see, Atkinson et al. (2003); Porter and Coltheart (2006); Mobbs et al. (2007)) another recent study evaluated a range of frontal executive functions including working memory and attention set-shifting. Results suggested impairment in frontal regions related to the executive tasks of attention set-shifting, working memory, and planning (Rhodes et al., 2010).

Due to the uneven nature of the cognitive profile in WS, studies have tended to discard some cognitive domains in favour of others that have been well illustrated, such as visuospatial cognition. Expanding current work to the frontal lobe should reveal additional phenotypes of the syndrome and their neurobiological underpinnings.

5.4 Language profile in WS

Although the earliest studies in language acquisition in WS have reported language deficits among WS patients Kataria et al. (1984), when examined in comparison to other cognitive domains and intellectual disabilities, language is well demonstrated in WS. This is due in part to the syndrome's intact language profile despite genetic deletion, craniofacial appearance, abnormality in brain growth, and other impairments in cognition. As these characteristics have major effects in DS patients, including language abilities, WS individuals have what is known as a "cocktail party personality" with a higher verbal rate and various linguistic skills associated with hyperfocus on the eyes of others during communication. However, WS individuals may exhibit difficulties in producing coherent speech as they shift from one topic to another; their speech resembling a disconnected cocktail-party speech (Lashkari et al., 1999).

During the early development phases of language acquisition, WS children experience a general delay in rhythmic patterns and first utterance (Mervis and Klein-Tasman, 2000). This suggests we explore rhythmic development in WS children through a brief exploration of motor skill development in order to have a clearer understanding of what may cause this reported delay in language onset. It is known that language development is highly connected to motor development: which is to say, language is a complicated system that embodies the sensory and motor systems. The neural motor system is connected to the vocal system, which requires muscle tone in order to

execute certain movements, or vocalization. In a longitudinal study, Masataka (2001) observed motor and language development in eight WS children, aged 6-30 months. Results demonstrated a general delay in motor and language onset, including canonical babbling and first words. Regardless of the variations in delay among subjects, hand banging was an indicator of canonical babbling across subjects. Rhythmic hand banging has been observed at the age of 74.50 weeks, canonical babbling at 76.50 weeks, and first word production at 98.50 weeks of age.

Previous abnormality in motor development results are delayed in early vocabulary acquisition. However, in comparison with DS children, WS 30-month-aged children showed a wider range of expressive vocabulary than DS patients. In early social communication, Laing et al. (2002) found a modest level of triadic interaction and poor levels of referential pointing and lack of pointing among WS children, despite their quantitatively larger vocabulary compared to the control group. Generally, language impairment in WS is relatively limited to early development of life and based on motor development delay; language impairment seems to disappear with age and language becomes independent from other cognitive deficits in WS.

Studies conducted of the language abilities of school-age and adolescents WS children reported a comparable outcome to typically developing individuals. Mervis et al. (1999) found that semantic categorisation among school-age WS children is similar to both DS and control groups. Nevertheless, one aspect of language is reported to be of difficulty among young and adult populations of WS. As we reviewed spatial representation deficits in the cognitive profile, spatial language was alos likely to be impaired. Bel-

lugi et al. (2000) indicate that WS individuals face difficulties in the use of spatial prepositions with a greater than 11% of errors compared to control groups.

The overall language profile of WS individuals indicates relative strength, in spite of other impaired cognitive domains, and among the syndrome's interesting aspects that can be further investigated at the neurobiological level are the correlation between visuospatial cognition and deficits in spatial language. Also of interest is and to what extent the dorsal pathway may contribute to these deficits.

5.5 WS and 7q11.23 duplication syndrome

The 7q11.23 duplication syndrome, or what is sometimes referred to as duplication of the Williams' syndrome region, is the opposite of chromosome 7q11.23 deletion. Interestingly, within the critical chromosome region both the deletion and duplication syndromes vary in their cognitive patterns and linguistic abilities, which should advance our knowledge of both syndromes and assist in identifying the genetic bases of the language profile in each syndrome. Although the investigation of the 7q11.23 duplication syndrome, which began in 2004, is far less advanced in its research than WS, it is possible to review salient characteristics of the syndrome at the physical and cognitive levels.

The first publication concerning the duplication syndrome did not find striking facial features as an aspect (Berg et al., 2007) of the syndrome, however, recent research indicates common craniofacial features across pa-

tients with the duplication syndrome, including a broad forehead, straight eyebrows, thin upper lip and a low insertion of the columella (Morris et al., 2015). Intellectually, 7q11.23 duplication syndrome patients experience developmental delay in learning, speech, and motor coordination (Berg et al., 2007; Morris et al., 2015). 7q11.23 duplication syndrome individuals demonstrate a very different social cognition profile compared to WS patients, and are subject to social anxiety, limited social interaction, and social isolation. Findings indicate that their strongest social interaction is limited to their families and close individuals (Velleman and Mervis, 2011; Earhart et al., 2016).

Unlike WS, language impairment is an important feature in the 7q11.23 duplication syndrome. Patient with duplicated 7q11.23 experience a general delay in speech and motor skills. Van der Aa et al. (2009) reported consistent findings of delay in language development across fourteen cases. While people with WS have strength in expressive language, duplicated 7q11.23 individuals are severely impaired in expressive speech. Somerville et al. (2005) reported the case of a child aged eight years with a severe expressive language deficit, including limited correct utterance of words; further, the receptive language rate was low, and expressive language was rated as severely impaired.

The aim of this section is not to tackle the 7q11.23 duplication syndrome in detail, but to present a brief exploration of cognition and language in the duplication of the same critical region as WS. In light of reviewed findings, the contradictory aspects of the comparative cognitive language profile in both syndromes is suggestive. Genetics are implicated in language im-

pairment, and thus far FOXP2 is specifically identified as implicated in certain language deficits. However, there are various cases, including WS and 7q11.23 duplication syndrome, where investigation at the genetic level should provide us with a clearer image as to what extent genetics are involved in language impairment. What is most promising here is that the identified region -the WS critical region- includes approximately 28 genes on chromosome 7 and these genes are also involved in the case of duplicated 7q11.23.

5.6 Discussion

The motivation behind this chapter is in part related to the previous chapter of DS. Although the nature of the two syndromes is different -DS syndrome is caused by trisomy of chromosome 21, whereas a deletion in 7q11.23 gives rise to WS- both syndromes share general features, such as craniofacial dys-morphism, brain growth abnormality, impaired cognitive profiles, and general developmental delay. Despite common features and impairments, WS individuals are hypersocial and their language profile appears to be intact. The asymmetry of language abilities in both syndromes, together with duplicated 7q11.23, is worth consideration.

At the hippocampal level, where we anticipate a contribution in language and cognition, research fails to report significant volume variations compared to normal subjects, however, alterations in synapses and metabolic reduction do occur (Meyer-Lindenberg et al., 2005b). This reinforces our hypothesis of hippocampal implication in language and cognition. As we reviewed in the DS chapter, morphological and synaptic alterations in the

hippocampal formation are present. And despite the strength of verbal short-term memory in WS, visuospatial capacity is severely impaired due to dorsal-ventral dissociation. This may also suggest multiple neural circuits in the hippocampus related to spatial cognition.

Although a wealth of evidence has formulated the WS phenotype, however, future efforts should focus on the genetic research to bridge the current gaps between genotype and phenotype by examining language impairment and its neurobiological bases. In the case of WS we find a convincing model of the relationship between genes and human cognition because a specific set of 28 genes has been identified as involved in WS and in the duplicated 7q11.23. For instance, it is interesting to know that, in mice, LIMK1 plays a prominent role in synaptic and dendritic spine growth in CNS and crucially alters dendritic spines morphology in the hippocampus. It is also suggestive that deleted CYLN2 mice exhibit slight deficit and abnormality in brain growth during the postnatal period. Yet, a straightforward correlation between these findings and the neuropathology of WS is not clearly illustrated.

Finally, one of the major limitations in imitative WS neurobiological studies is the tendency to compare WS individuals to healthy subjects; alternatively, other syndromes such as duplicated autism, DS, fragile X and duplicated 7q11.23 are also of significant importance.

Chapter 6

Schizophrenia, Depression and Bipolar Disorder

6.1 Introduction

Schizophrenia is a chronic neurological mental disease, which was discovered by Eugene Blueler in 1908 and is characterised by abnormal social and emotional behaviours associated with illusion, irregular cognitive functions, and language deficits. Early and late onset of the disease rarely occur, while average onset occurs between the late teens and mid thirties with a prevalence of 1% worldwide (Rahman and Lauriello, 2016). Diagnosis of schizophrenia is based on predominant symptoms including cognitive and language deficits. Schizophrenia symptoms are classified into two categories: positive symptoms, which refer to an excessive function of various cognitive domains such as delusion and thought disorder, and negative symptoms, which refer to a decline in specific cognitive domains, including decreased speech skills and lack of social cognition.

An important biological indicator in the nature of SZ is the distortion of the frontal or temporal-hippocampal connection. Indeed, if impairment is to be addressed in the context of SZ's underlying causes, it is worthwhile considering those neural substrates in relation to language processing. The question in this chapter concerns whether frontal-hippocampal interaction plays a role or not, based on our hypothesis.

6.2 Structural brain alterations in SZ

The underlying basis of SZ is still under investigation. However, research findings have revealed early structural anomalies in both grey and white matter and in the neural network throughout the brain. Various hypotheses have been argued to illustrate SZ the mechanism of SZ. In a top-down approach, a clear deficit in information processing led to special attention on suspected hubs, including the frontal lobe. Several studies have been devoted to abnormality within the frontal lobe and its connectivity to other cortical and subcortical structures.

Dysfunction within the frontal cortex is often assigned to the dorsolateral prefrontal cortex (DLFC). From hypofrontality (Curtis et al., 1999), to hyperfrontality activation in the DLFC (Callicott et al., 2000), research has associated both forms of activation with poor performance in working memory. In contrast, Callicott et al. (2003b) reported intact working memory among schizophrenic patients despite greater and less activation in the DLFC. Likewise, individuals who are at greater genetic risk for schizophrenia can exhibit overactivation in the dorsal pre-frontal cortex with the absence of cognitive impairments (Callicott et al., 2003a; Salgado-Pineda et al.,

2007). It has been suggested that SZ symptoms are due to "miswired" connections between brain regions, rather than specific structural impairments (Goodman, 1989). In a resting state, or default mode network (DMN), the posterior cingulate, precuneus inferior parietal lobe, and the medial prefrontal cortex are activated, and self referential processing, while suspended in task solving and interacting with external world (Raichle et al., 2001). Illustrating abnormal aspects of the DMN in anatomically related regions in SZ individuals, fMRI data have revealed irregularity within grey and white matter and altered connectivity in the medial frontal lobe (Camchong et al., 2011).

Due to its central role in executive functions and cognition, the frontal cortex has been considered by previous studies as crucial for its connections to other regions of the brain. However, other research has looked at the brain from a wider perspective, namely, at the overall activation of remote structures and to what extent strong integration can be impaired. It is relevant that neurons act as a cohort in the accomplishment of tasks. In the case of schizophrenia, Foucher et al. (2005) refer to the integrated system as the "core" and non-integrated systems as"the rest". Both terms were presented by Tononi et al. (1998) and their referents described as task-dependent; it was observed that the "core", or "functional cluster", is highly activated among certain subset regions during specified tasks, more than "the rest" of the brain. From this perspective, there are two hypotheses about what occurs in SZ: 1) the core is impaired and exposed to irregular noise from the rest, and 2) the rest is activated to such an extent that it interferes with the core. Foucher et al. (2005) have tested these hypotheses in lexical decision and retrieval tasks. Their findings indicate that both SZ and

control groups did not show any differences in core activation during these tasks, and interpretations concluded that the core was affected by an over-integration with the rest. The modularity of language in the brain imposes a specific manner of examining frontal and temporal lobe circuits, which are specifically located in the Broca's and Wernicke's areas. Regardless of cognitive and linguistic outcomes, EEG data evidenced a clearly reduced coupling between the frontal and temporal lobes during SZ patients' speech production, compared to a healthy matched group (Ford et al., 2002).

In addition to the dominant prefrontal cortex hypothesis, robust morphometric analysis has introduced the hippocampus as the seat of a major brain abnormality in SZ. The medial temporal lobe, including the hippocampus and the amygdala, has been well documented in SZ. According to these measurements schizophrenic patients manifest volumetric alterations from the normal. Seidman et al. (2002) found a negative association between the hippocampus and verbal declarative memory, and SZ patients showed an abnormal and smaller left hippocampus compared to controls, although causes for this abnormality are unknown. In order to understand the variations in function and morphology among subcortical regions, van Erp et al. (2016) carried out a meta-analysis study using MRI scans, which looked at 2,028 SZ patients and 2,540 healthy controls. Interestingly, the work devoted to subcortical abnormality indicated a prime differentiation in the hippocampus between both groups. SZ patients tended to possess significantly smaller hippocampus, amygdala, thalamus, accumbens and intracranial volume (IVC) and larger lateral ventricle volumes, pallidum and putamen (Figure 6.1). Current meta-analysis confirms previous results by Wright et al. (2000), which evaluated cortical and subcortical volumetric variations among 1,588

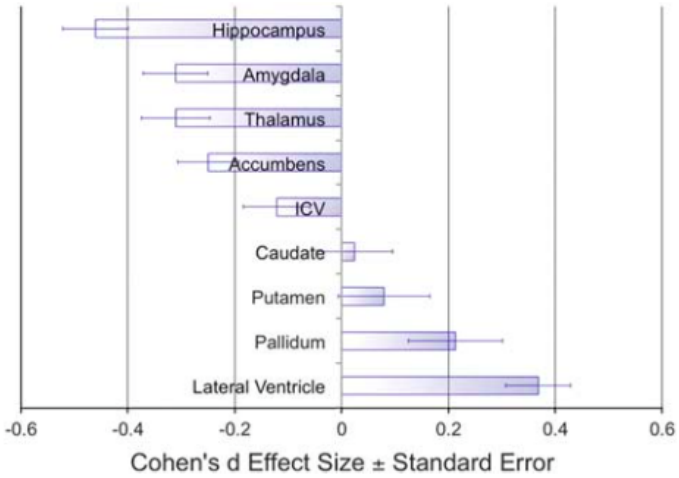


Figure 6.1: Cohen's d effect size shows robust patterns of subcortical structures volume in SZ individuals compared to controls. Adapted from (van Erp et al., 2016). Cohens d effect size suggests that d=0.2 be considered a "small" effect size, 0.5 represents a "medium" effect size and 0.8 a "large" effect size.

SZ patients and matched controls. Overall findings indicated a slight reduction in the cerebral volume in SZ, however, a greater reduction was noted in the medial temporal lobe. When considering a volume of 100% in the control group, SZ individuals show 93% in the left and 95% in the right hippocampus.

Indeed, diversity in approaching this hippocampal abnormality led to a focus on the condition as a central pathophysiology of SZ. Common results across studies indicate a major alteration in synaptic circuits within the hippocampus and in its connection to the prefrontal cortex (see several approaches in Harrison (2004)). Although reduction in the hippocampal volume does not entail a sharp reduction in neuron density, as is characteristic of AD, or in the case of DLPFC in SZ (Figure 6.2), several neurochemical hypotheses about SZ have been addressed. An important characteristic of

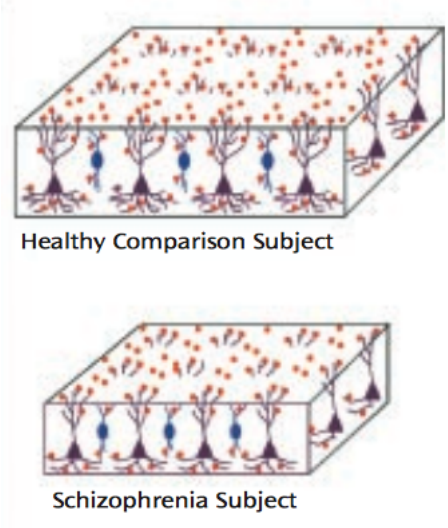


Figure 6.2: Neuronal loss in the dorsolateral prefrontal cortex in SZ patients compared to healthy individuals

the hippocampal formation is the role of the DG, which is associated with the impairment of glutamatergic neurotransmission (Heckers and Konradi, 2002).

Previous reviews have demonstrated impairment in the frontal cortex and the hippocampus independently. Nevertheless, the hippocampal-prefrontal cortex (H-PFC) interconnection poses a singular challenge to revealing its implication in SZ. A large body of literature highlights deficits in the H-PFC circuit in various psychiatric disorders. Signal transmission in H-PFC is composed of multiple routes by multi-routes from the hippocampus to the PFC. In mice models, hippocampal projection is initiated from CA1 and the subiculum to orbital regions including the PFC (Cenquizca and Swanson, 2007). Likewise, a lesioned hippocampus in macaque monkeys resulted in a significant reduction in the hippocampus, and lesion abnormality was detected in the fornix and ventromedial prefrontal white matter. Indeed

differences in the prefrontal cortex across animal species cannot yield on its own a complete understanding of the neural organization and circuitry of the H-PFC. Nevertheless, to a certain extent, a complementary role of animal models illuminates our understanding of brain interaction complexity. For instance, during spatial working memory tasks, the synchronization measurement of H-PFC connectivity varies: wild-type mice exhibited increased synchrony during the task, whereas, in Df(16)A1 $^{+}/^{-}$ mice, synchrony was significantly reduced due to microdeletion on chromosome 22 (q22.11.2).

In addition to the prefrontal disturbance, another attempt to understand substrates of positive and negative cognitive symptoms associated the hippocampus with the temporal-pariental occipital junction (TPJ). In SZ, the TPJ is believed to be overactivated and coupled with a hippocampal overactivation, which in turn gives rise to abnormal social cognition (Wible, 2012).

6.3 Cognitive profile in schizophrenia

One of the salient cognitive characteristics of SZ is social cognition, which involves conceptualization of one's attitude towards oneself and social interaction, with others. Social cognitive impairment in SZ is not segregated from other deficits in memory, attention, and problem solving. Social cognitive research in SZ has tackled the issue under four categories: emotion processing, social perception, attributional bias, and theory of mind (Green et al., 2005; Penn et al., 2006, 2008). In a meta-analytic review of 86 studies of emotional perception abilities, across various tasks of perceiving and recognizing facial emotions, SZ individuals were significantly impaired com-

pared to controls (Kohler et al., 2009). The psychophysiological marker of visual attention suggests that SZ patients tend to have a "restricted" scanning method that omits essential facial features, such as the eyes, nose, and mouth, that highly indicate one's emotional state. Likewise in a meta-analysis using theory of mind, results showed various alterations occur in large-effect sizes in schizophrenia.

General memory impairment is often found in SZ, specifically, in long- and short-term memory. Retrieval declarative memory has been reported to be consistently impaired, whereas procedural memory seems to be less affected (Goldberg et al., 1989, 1990, 1993; Takano et al., 2002). SZ individuals also exhibit late response and impaired semantic memory (Chen et al., 1994; McKay et al., 1996). Characteristics of memory performance in SZ raise questions concerning another related cognitive function. various scholars suggest that processing speed is relativity slow in SZ individuals (Brébion et al., 1998); (Knowles et al., 2010). Nevertheless, one of the long-standing dogmas of the field is that cognitive impairment in SZ is a consequence of dysconnectivity in the brian. Alloza et al. (2016) hypothesize that information processing is a dominant component, which highly attenuates other cognitive and intellectual capacities. Their findings propose that, neuroanatomically, white matter integrity is essential to accelerate general cognition vis information processing.

Interestingly, in a neuroanatomical comparison between working and long-term memory tasks, data has revealed that the right DLPFC in SZ individuals showed impaired activation in both tasks. Hippocampal activation was equally impaired.

Attention is another major deficit in SZ. During attention tasks, neuroimaging research has indicated that SZ patients show high activation in specific brain regions, whereas other studies report decreased activation. Such a difference in volitional activation may due to experimental designs, whether for transient and sustained phases of attention. In a study that aims to avoid previous conflicts in data, Carter et al. (2010) carried out fMRI, which segregated analysis of transition and sustained stages of attention in SZ patients and healthy controls. The results indicated that the SZ group performed with a significant error rate and slow responses, relative to controls. At the brain level, both groups displayed activation in core attentional networks including the anterior cingulate gyrus, the dorsolateral prefrontal cortex, insula and inferior parietal sulcus. Analysis revealed that SZ patients showed a greater activation in previous brain regions than controls. However, during transient phases, lower activation among SZ group has been reported.

6.4 Language profile in schizophrenia

Language profile in SZ is a thorny issue that has been argued in various ways. A popular method is to discuss language within the context of thought, and several studies have argued the issue of language deficit in SZ individuals under the long-standing philosophical debate of language and thought. This debate elusively attempts to build a tight relationship between language and "thought disorder"; an approach which is unlikely to provide us with clear results. One perspective of significant importance addresses biological and neurobiological alterations in SZ. Neurobiological alterations give rise to a range of cognitive deficits that are implicated in language processing and

should be taken into account in research.

Hence, in this section we aim to relocate language deficits in SZ so that they parallel what has been investigated at the biological level. Two major hypotheses are argued in language and SZ research. The first hypothesis considers the SZ individual's language as a consequence mainly of semantic memory impairment (Spitzer, 1993). The second hypotheses proposes that SZ language impairment is due to a dysfunction in flexibility within a certain context (Cohen and Servan-Schreiber, 1992). Both hypotheses are worth considering given that their potential biological underpinnings are affected during the course of SZ. The first hypothesis posits that a semantic memory network is essential in SZ language production. It is often reported that SZ individuals display a tendency to follow strings of related words, which results in a weak coherence in speech (Bleuler, 1950). Biologically, the hippocampus has been investigated as a major hub for semantic memory and language processing, (Ullman, 2015) thereby suggesting a link to SZ. And in fact, several studies have found H-PFC dysconnectivity among SZ individuals (Harrison, 2004).

Although the first hypothesis is relevant to our main hypothesis, the second theory is more related in two aspects. Firstly, a wealth of evidence indicates the wide range of cognitive deficits includes flexibility and set-shifting, and recent studies have highlighted the distinct role played by subcortical-PFC circuits in facilitating behavioural flexibility (Floresco et al., 2009). Previous findings have enhanced our hypothesis concerning the major role of the hippocampus in language processing and flexibility. Secondly, models suggest that functional deficits can be illustrated as a biological disturbance,

such as dopaminergic irregularity in the frontal lobe. In a following chapter we will argue that neurotransmitters play a vital role in subcortical structures as well as the cortex.

In general, there are robust findings of language impairment in SZ. While several studies tend to associate that impairment with thought disorders, we believe that the impairment in language is biologically evident and must be considered as a concrete referent supporting attempts to extend the language network in the brain.

6.5 Depression and bipolar disorder

Recently, interest has been directed towards a hot hippocampus, which is implicated in cognitive functions that include emotions, anxiety and a behavioural expressions of depression (Fanselow and Dong, 2010). Within the course of biological stress within the medial temporal lobe, in particular, the hippocampal formation is a hub that undergoes variable degrees of genetic, molecular, connective, and functional alterations.

Based on various psychiatric conditions, major depression (MD) and bipolar disorder (BD) have been heavily investigated in order to uncover genetic and neural alterations and their cognitive manifestations. Whilst the main focus of previous research has been devoted to emotional symptoms, recent attention has been directed towards cognitive dysfunction (CD) across depressive and anxiety disorders (Millan et al., 2012).

Available data from MD cognitive and language dysfunctions in comparison to BD dysfunctions are relatively limited. Hence, this section aims to shed more light on the cognitive/language profiles in both MD and BD. Although BD is not considered in the index of stress-related disorders, molecular genetics show an association between MD and BD. Given that the medial temporal lobe is likely to be affected, it follows that there are hippocampal abnormalities in both disorders. I intend to focus on the consequences of the hippocampal alterations and dentate gyrus neurogenesis in cognitive and language impairments. We will review main functional findings and the occurrence of alterations in the hippocampus, followed by cognitive and language deficits as phenotypes in both disorders.

Despite the resemblance of hippocampal architectures across primate and rodent brains, human hippocampal formation maintains substantial differences, including density of cell layer in the CA1 and the mass growth of the entorhinal cortical subdivisions, when compared to monkey and rat hippocampal neuroanatomy (Anderson et al., 2007).

Morphological changes and loss in hippocampal volume during the course of MD and BD have been detected in multiple studies (Sheline et al., 1996; Sheline, 2000; Frodl et al., 2002; Bremner et al., 2000; Videbech and Ravnkilde, 2004; Simonetti et al., 2016). Although, the direct causes of hippocampal volume reduction in MD and BD remain undefined, one speculation holds that hippocampal neurogenesis dysregulation in the dentate gyrus may play a role in this shrinkage (Kempermann, 2002; Lee et al., 2012a). Negative regulation of adult hippocampal neurogenesis is induced by an increased glucocorticoid level in the brain. Given that glucocorticoids function in

neuronal survival in hippocampal neurogenesis (Sousa et al., 1998; Sapolsky, 2000; McEwen, 2001), glucocorticoid is highly expressed in the hippocampal formation compared to other brain structures (Cereseto et al., 2006).

In contrast to the lowered regulation caused by stress, evidence from antidepressant treatments suggest there is enhancement in hippocampal neurogenesis in parallel with behavioural performance in animal models (Manev et al., 2001; Drigues et al., 2003; Santarelli et al., 2003).

6.6 Cognitive profile in MD and bipolar disorder

Cognitive deficits are a common occurrence in MD and bipolar disorder (Goodwin, 1997; Lee et al., 2012b; Wagner et al., 2012; Butters et al., 2000), and this section reviews several cognitive dysfunctions reported in MD and BD. Neurophysiological impairments in the brain should indicate various cognitive consequences. In set-shifting, individuals require a cognitive flexibility that involves the capacity to switch between one task and another, this flexibility generates a rapid adaptation to various patterns based on the task. In MD and BD findings indicate inflexibility in maintaining set-shifting (McKirdy et al., 2009; Lockwood et al., 2002), as well as planning and problem-solving impairments (Purcell et al., 1997; Naismith et al., 2003).

In cognition, mental flexibility enables one to shift action and/or thought in co-current situations. Circumstances of the context require rapid cognitive adaptation and interaction supported by seductive controls in the prefrontal lobe and related brain regions. In MD and BD, patients are im-

paired in mental flexibility tasks relative to control groups (Purcell et al., 1997; Airaksinen et al., 2004; McClure et al., 2005; Schouws et al., 2009).

Recently, neurobiological evidence has challenged previous theories of hippocampal implications in declarative memory. In fact, the hippocampus is a hub of cognitive flexibility that involves several domains. For instance, fMRI findings reveal a bilateral hippocampal activation in relational learning across short delays. (Ranganath and D'Esposito, 2001; Hannula and Ranganath, 2008). Likewise, comparative neurobiological studies have provided convergent evidence. The neurogenesis of granule cells in the dentate gyrus of the hippocampus plays a prominent role in both adaptation (Wiskott et al., 2006) and spatial flexibility (Pastalkova et al., 2008; Garthe et al., 2009; Burghardt et al., 2012).

Decreased speed of information processing has also been reported among MD and BD patients due to neuropsychological alterations (Nebes et al., 2000; Tsourtos et al., 2002; Den Hartog et al., 2003; Gildengers et al., 2012; Halari et al., 2013).

Generally, an MRI enables us to detect alteration in various brain regions in cognitive decline. Information-processing speed is distributed over cortical and subcortical structures. The correlation between the hippocampal volume reduction and memory deficits is well established (Giménez et al., 2004; Mungas et al., 2005; Ystad et al., 2009). Similarly, white matter consists of pathways connecting various brain regions, and including myelination, which contributes to cognition and regulation of information processing speed. (Gunning-Dixon and Raz, 2000; Fields, 2008; Prins and Scheltens,

2015). Normal aging as a factor of slowness in information processing indicates an increase in white matter hyperintensity and reduced hippocampal volume Papp et al. (2014).

Although white matter and the hippocampus have been treated individually, Papp et al. (2014) compared the speed processing of cognitive controls in dual neurobiologiacl alterations of normal aging, finding increased white matter hyperintensity and reduced hippocampal volume. Findings suggested large white matter hyperintensity volume and reduced hippocampal volume give rise to a slower execution in cognitive performance (Papp et al., 2014).

In sum, findings across cognitive disturbances in studies of MD and BD show cognition to be impaired with alterations in set-shifting, cognitive flexibility and information processing speed. Patterns of performances in previous work neurobiological underpinnings are implicated in these deficits. Considerable evidence has shown abnormalities in cortical/subcortical structures at the dynamic and large-scale connectome level. What is relevant to this thesis is the implication of the hippocampus in cognition and language deficits in MD and BD. The human brain is organized in a sophisticated network of connections, and taking into account hippocampal abnormality as an early sign of these conditions may provide us with some knowledge of the cognition substrate including language and communication deficits.

6.7 Language profile in MD and bipolar disorder

Neuropsychological studies of MD and BD have mainly focused on certain cognitive aspects, such as attention and set-shifting. To show related ab-

normalities in language processing in comparison with schizophrenia, for instance, few studies have investigated language impairments and their neurobiological characteristics in MD and BD. What has been carried out in other cognitive domains should generate curiosity and investigation in language processing, yet lack of evidence about language processing in MD and BD has led to contradictory conclusions. Event-related potentials (ERPs) of EEGs have been widely utilized in language comprehension, semantically and syntactically. Two main components of ERPs are attributed to each aspect of comprehension: N400 is a negative-going wave deflection that peaks around 400 milliseconds post-stimulus onset and that often responds to semantic violation, whereas a P600 positive-going wave response is associated with incongruent syntactic structures (Kutas and Hillyard, 1980; Friederici et al., 1996; Kutas and Federmeier, 2000; Luck, 2014). Findings in a visual experiment of semantic violations did not detect alterations or an increase in N400 ERP amplitudes among depressed patients (Deldin et al., 2006). Likewise, in congruous/incongruous semantic tasks, MD patients showed the deficits and slower reaction times associated with latency in N400 amplitudes (Iakimova et al., 2009). Ryu et al. (2012) detected a larger N400 amplitude in congruous words in BD patients. Inconsistent with a previous study, Cermolacce et al. (2014) showed deficits in natural speech semantics, but no differences in the N400 component were observed.

Among BD patients, syntactic structures within sentence comprehension seem to be abnormal. Recent work by Lee et al. (2016) compared patients with schizophrenia to BD; electrophysiologically, both groups showed less than P600 amplitudes relatively to healthy subjects in instances of incongruous syntax.

fMRI edvidence from BD patients has indicated consistent implications of various brain regions during linguistic tasks. And the overarching concern in studies of brain activation has been towards the prefrontal cortex. Along with significant decreases in reaction times, Curtis et al. (2007) found alterations in the left PFC. Prefrontal, striatal and default mode network during verb fluency task (Costafreda et al., 2011). As previously mentioned several studies focused on the functional neuroanatomy of cognitive controls, rather than the language networks in MD and BD. To remedy this situation, it is worthwhile considering related subcortical structures, which may identify a clearer image of the language network. For instance, a growing body of evidence suggests involvment of the medial temporal lobe, including the basal ganglia and the hippocampus in language processing (Duff and Brown-Schmidt, 2012; Ullman, 2015).

Recent interest in hippocampal amnesia highlights disturbances in online language interactions (Duff et al., 2009; Duff and Brown-Schmidt, 2012; Rubin et al., 2014). During online processing, language usage requires a high level of flexibility in order to produce and/or combine novel expressions in immediate interpretation. Findings from Duff et al. (2009) show that hippocampal amnesic patients uttered less verbal play compared to control groups. By contrast, verbal play remained intact in the case of a damaged ventromedial prefrontal cortex (Gupta et al., 2012). Although the hippocampus is often treated in the context of memory, Hasson et al. (2015) suggest that memory and ongoing processing are neurobiologically integrated through reshaped synapsis by previous knowledge.

Likewise, in the subcortex contribution in language, a reinforcment of the thalamus as a key component in language network has been addressed in numerous studies De Witte et al. (2006); Klostermann et al. (2015); Theofanopoulou et al. (2016). EEG data has indicated that the activation of the thalamus coincides with cortical activation during syntactic and semantic tasks (Wahl et al., 2008), as well as indicating the role of basal ganglia in speech motor control (Booth et al., 2007; Murdoch, 2001).

6.8 Discussion

This chapter is an attempt to shed light on several mental disorders: SZ, MD, and BD. And a review of the literature has highlighted several issues that can be discussed in order to bolster and refine my assumption about the neurobiological bases of language processing.

Compelling evidence indicates that each of previous chronic disorders are implicated in profound cognitive and language disturbance. Biologically, research outlines the relationship between those impairments and specific brain structures. The problem, however, is that one encounters numerous studies dedicated to a cognitive top-down approach and devoted to the frontal cortex, whereas in SZ, for example, various irregularities in the MTL have been reported. And while it is indeed true that the frontal lobe plays a significant role in cognition, I believe, however, this importance is not independent from the MTL.

Well-delineated language deficits across the discussed disorders posit the need to extend our knowledge of language processing as it occurs in vari-

ous brain regions. As SZ individuals characteristically display substantial deficits in real-time communication, this has led to a tendency to account for the phenomenon as "thought disorders" in the SZ language profile. This in part has been the stance taken by the field of psycholinguistics in which researchers associate words in the patient's dominant language with psychological analysis. We suggest that cognitive neuroscience, current clinical data, and further research on the MTL will provide sufficient perspective to improve the field of the neurobiology of language, and that they will solve part of the puzzle of language.

Finally, psychiatrists define SZ as a "dopamine disorder" due to the condition's major alterations in dopaminergic transmission in the cortex and subcortex. Nonetheless, we propose that dopamine is essential not only in the context of learning and reward, but also in other cognitive and linguistic aspects, which are further explored in (Hippocampal function in cognition) chapter.

Chapter 7

Concluding remarks and future directions

The goal of this thesis was to reinforce the hypothesis that there is a wider language network in the brain that encompasses the subcortex. Although subcortical structures have been largely omitted in prominent language models in neurobiology, recent evidence from animal models has highlighted the significant role played by the basal ganglia (area X in songbirds) along with cortical subdivisions in learned vocal communication (Nottebohm et al., 1976; Jarvis et al., 1998). This thesis goes beyond the precedent and suggests the role of the hippocampal declarative memory in online language use by reviewing language profiles in various pathologies and diseases that affect the hippocampus. I aim to present the hippocampus as a multi-cognitive operator. The hippocampus has been frequently associated with navigation and memory, and in the thesis I introduce the creative and flexible mechanism created by the hippocampus to support multisensory and interactive process during online language use. Indeed, the proposal leads to a similar

hippocampal model of relational binding as that which serves spatial navigation; the model is applicable not only in spatial cognition but might also be emulated in the context of language use. In other words, I suggest there is a shared neural mechanism for memory and language in a relational binding fashion. This hippocampal mechanism is capable of creating a flexible map in independent contexts based on previous stored memory, which enables us to retrieve the past, generate predictions, and adapt to a certain discourse.

The thesis aims to support the crucial role played by the hippocampal declarative memory system in language by reviewing language deficits and their links to hippocampal alterations in various pathologies. Findings from previous chapters indicate that the hippocampus affects language at two levels. First, in the general delay in language acquisition and other cognitive aspects, and second, in the disturbed use of language during online communication and short lag interaction is seen to occur when the hippocampal formation is lesioned. It appears that hippocampal lesions suppress the flexible use of stored information within a certain context in communication, as it does in flexible navigation in animal models.

Although the hippocampus is one of the most investigated structures in the brain, there is a general lack of investigation in its role beyond memory which has limited our understanding of its function and potential. On the other hand, animal models have advanced our understanding of the hippocampus via resembled mechanisms of relational binding during spatial tasks, namely, grid and place cells. These mechanisms indicate that we may benefit from the formation of hippocampal relational map during language processing and how memory and language interact together to serve rapid

processing of communication.

Given that the overarching concern in the neurobiology of language is focused on the neocortex, the role of subcortical structures remains hotly debated. To yield a clearer understanding of the hippocampal contribution to language, future studies may exploit advanced research techniques, including fMRI, to identify the interaction between the hippocampus and the prefrontal cortex during real-time language processing. EEG methods which yield gamma oscillations warrant further investigation during online language interaction. Likewise, the interaction between declarative and procedural memory systems in both forms of cooperation and competition is a crucial step to reinforcing the idea that the biological underpinnings of memory systems should not be isolated from model of language, and in turn, will lead to an extended understanding of the neurobiological network of language in the brain.

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