Schematic Representation Across Age and in Patients with vmPFC Lesions

by

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A thesis submitted in conformity with the requirements for the degree of Master's of Arts in Psychology

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Abstract
This study tested the mechanism of the ventromedial prefrontal cortex (vmPFC) in representing schemata, be it excitatory or inhibitory. Participants were administered a behavioural task distinguishing their ability to activate a relevant schema from their ability to inhibit an irrelevant schema. Healthy participants were highly accurate throughout the task, indicating proficiency in both abilities. However, older adults demonstrated a need for greater cognitive resources to inhibit a previously relevant schema. Non-confabulating patients with vmPFC lesions acted similarly to control participants, while patients with vmPFC lesions with either current or prior demonstration of confabulation performed abnormally. Specifically, their inability to inhibit irrelevant schemata was more severe than their inability to activate a relevant one. The results suggest that the nature of vmPFC damage leading to confabulation may also be responsible for erroneous schema representations. A sub-region of the vmPFC is proposed to underlie the representation of schemata through semantic lateral inhibition.
Acknowledgments

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Chapter 1: Introduction

From an evolutionary perspective, the advantage offered by memory is the ability to predict future outcomes, thus informing our decisions and ultimately our behaviours (Klein, Cosmides, Tooby, & Chance, 2002; Kroes & Fernández, 2012). When encountering a new situation, one need not actively recall all previous situations that are similar in order to determine how best to respond. One instead relies on a general representation of the situation, which has been assembled based on the commonalities between many similar, repeated events (Klein, Cosmides, Tooby, & Chance, 2002; Kroes & Fernández, 2012). This general representation is called a “schema.”

Specifically, a schema is a higher level cognitive knowledge structure encapsulating lower level representational elements derived from long-term memory (i.e. concepts). This definition arises from unifying trends of a century of adaptations of the idea. For instance, the term “schema” was originally proposed by Head and Holmes (1911) to reference a standard that results from previous information against which one compares new information to detect changes. Early development of the idea of “schema” comes from writings by Piaget (1926), in which a schema referred to a “general form,” lacking detail, and composed of multiple features that are consistently perceived together. Bartlett (1932) later defined “schema” as a cluster of organized past reactions or experiences. He noted that there is considerable overlap between the elements composing different schemata and thus that schemata are interconnected and organized together. Posner and Keele (1968) refined this definition, stating that schemata are the commonalities among a set of patterns, abstracted during learning. Recently, the term “schema” has been established as referring to a relevant mental framework, or “prior associative network,” with which new information can be understood (Tse et al., 2007; Van Kesteren, Fernández, Norris & Hermans, 2010; Wang & Morris, 2010).

The term “schema” must be distinguished from the highly related idea of “concept.” The term “concept” is meant to represent a set of features of a particular class of entities. Concepts are the elements composing a schema (Chan, Chiu, Lam, Pang & Chow, 1999), although they need not be part of one. For example “going to a restaurant” could represent a schema, while “the bill” would represent a concept within that schema (Bower, Black & Turner., 1979; Chan, Chiu, Lam, Pang & Chow, 1999). “Concepts” in this case are synonymous to Bower and colleagues’ (1979)
“high-frequency events” within scripts, and with Schank and Abelson’s (1977) “main conceptualizations,” which were defined as events that are essential within a given general scene. According to Bower and colleagues (1979), “central events” (or “concepts”), should act as a powerful probe to call up the script (or “schema”) from one’s memory.

The function of schemata is two-fold. Firstly, they guide behaviour, and secondly, they assist memory, acting as a substrate for acquiring new memories and assisting in retrieval through the process of reconstruction. In the former case, schemata guide behaviour by treating novel elements in terms of these higher-level experience-dependent cognitive structures (Kumaran, Summerfield, Hassabis, & Maguire, 2009; Shea, Krug, & Tobler, 2008). In the latter case, schemata facilitate the encoding of new memories by transforming them to higher level representations (Carmichael, Walter, & Hogan, 1932) and enhance memory retrieval by employing an existing schema to reconstruct important but unavailable information (Anderson & Pichert, 1978).

Both of these functions of schemata are thought to be mediated in part by the ventromedial prefrontal cortex (vmPFC). Kumaran, Summerfield, Hassabis, and Maguire (2009) found that a functionally coupled circuit involving the hippocampus and vmPFC underpins the emergence of conceptual knowledge and its effect on choice behaviour. This finding is supported by the well-established implication of the vmPFC in decision-making and the prediction of future outcomes (Bechara, Damasio, Tranel & Damasio, 1997; Bechara, Tranel, Damasio, & Damasio 1996). There is also evidence of the involvement of the vmPFC in assimilating new representations into existing schemata, thus facilitating encoding (Tse, Takeuchi, Kakeyama, Kajii, Okuno, Tohyama, Bito & Morris, 2011; Van Kesteren, Fernández, Norris & Hermans, 2010). In addition, the vmPFC may underlie the reconstructive faculty of schemata in memory retrieval, as damage to the vmPFC is sufficient to cause confabulation (Gilboa & Moscovitch, 2002), a unique memory disorder involving the retrieval of erroneous memories associated with a lack of awareness of their falsehood (Moscovitch, 1989). Confabulation is said to involve a magnification of existing “normal” misremembering instances (Bartlett, 1932; Fotopoulou, 2008). Specifically, it is suggested that confabulation shows similar patterns of omission, distortion, and fabrication as observed in normal memory reconstruction, albeit to an exaggerated degree.
The diverse cognitive processes supported by the vmPFC appear to be unified by their involvement in the dynamic functions of schemata. As such, it has been proposed that the responsibility of the vmPFC may be to abstract key features of relevant past situations, evaluate possible future outcomes, and trigger the appropriate physiological and emotional responses as suggested by this evaluation (Kroes & Fernández, 2012; Roy, Shohamy, & Wager, 2012).

The confabulation literature provides support for the proposed general function of the vmPFC. Assuming the proposal to be accurate, then inaccuracies in the general representation upon which future outcomes are evaluated would yield inappropriate behaviour. In other words, one might expect these individuals to display contextually dysfunctional behaviour, no longer likely to improve the outcome of a situation. Indeed, this is observed in confabulating patients who act in accordance with their erroneous memory representations (Schnider, Ptak, von Däniken, & Remonda, 2000). This finding strengthens the foundation for the proposed function of the vmPFC when considered along with the association of confabulation with vmPFC damage (Gilboa & Moscovitch, 2002) and the suggestion that this memory disorder is influenced by pre-existing schemata (Burgess & McNeil, 1999; Burgess & Shallice, 1996).

As further evidence in support of the recent proposal regarding the general function of the vmPFC, one might note that this contextually inappropriate behaviour is not observed in amnesic individuals with hippocampal damage. In contrast, these patients often depend on current context to determine how best to behave in order to compensate for their memory impairment for recent events (Wilson & Watson, 1996). As the vmPFC in such individuals would be spared, this observation is congruent with the idea that schemata represented by the vmPFC are relied upon to adapt behaviour.

Research surrounding the recently formulated memory transformation hypothesis constitutes a final line of evidence that will be presented to corroborate the general function of the vmPFC depicted above. According to the memory transformation hypothesis, as representations of long-term memories progress from hippocampal to extra-hippocampal structures, they become “schematized”, meaning that they undergo a loss of detailed, contextual features (Winocur & Moscovitch, 2011). It is further suggested that memories that retain contextual details continue to be critically supported by the hippocampus. The memory transformation hypothesis was proposed in part as an alternative to the standard consolidation theory which states that both
episodic and semantic memory are initially stored in the hippocampus and are reorganized over time into a distributed extra-hippocampal network (Squire, 1992; Alvarez & Squire, 1994). According to this latter theory, the memories themselves remain essentially unchanged with consolidation and only their underlying neural substrates are significantly altered (Squire, 1992; Alvarez & Squire, 1994).

The process of memory transformation could be the mechanism for abstracting commonalities from episodic events stored in the hippocampus in order to generate a schema that would be represented by the vmPFC. This possibility is supported by the finding that with repeated tests of recognition over time, there is an increase in activity in the vmPFC that is correlated with a decrease in activity in the hippocampus (Takashima et al., 2006). While this result could also be accounted for by the standard consolidation theory, recent evidence of the implication of the vmPFC in representing schemata converge towards the memory transformation hypothesis as the more likely explanation (Nieuwenhuis & Takashima, 2011; Tse, Takeuchi, Kakeyama, Kajii, Okuno, Tohyama, Bito & Morris, 2011; Van Kesteren, Fernández, Norris & Hermans, 2010). In order to empirically test the hypothesized function of the vmPFC, its role in representing schemata needs first to be delineated. Several studies have demonstrated its implication in the creation of schemata and its role in assimilating information into pre-existing schemata (Tse et al., 2011; Van Kesteren, Fernández, Norris & Hermans, 2010). In addition, some have hypothesized that the region may serve an inhibitory role (Nieuwenhuis & Takashima, 2011), which has yet to be tested. It seems that there are two possibilities. Either the vmPFC is responsible for the activation of relevant pre-existing schemata, or alternatively, it is responsible for the inhibition of schemata and concepts irrelevant to the current situation. The confabulation literature appears to support the proposed inhibitory role as confabulation may result from damage to the vmPFC (Gilboa & Moscovitch, 2002) and has also been suggested to arise from an inability to inhibit irrelevant schemata or memory traces (Burgess & McNeil, 1999; Burgess & Shallice, 1996; Schnider & Ptak, 1999).

As a prelude to this investigation, it is important to review the major findings regarding 1) the role of the vmPFC in schema-dependent memory processes, 2) the relationship between confabulation and schematic representation, and 3) the implication of schematization in memory transformation.
1.1 vmPFC and schema-dependent memory processes

Several studies indicate that the vmPFC is implicated in the assimilation of new information into previously existing schemata (Tse et al., 2011; Van Kesteren, Fernández, Norris & Hermans, 2010). Others assert that the vmPFC is responsible for inhibiting irrelevant pre-existing representations (Nieuwenhuis & Takashima, 2011). It appears possible for the vmPFC to support both processes. While the former has been demonstrated in several studies, the latter has only been hypothesized, yet to be tested experimentally. It seems possible that the vmPFC may not play an inhibitory role, but may merely serve to select and activate the schema most appropriate to a given situation.

Support for the assimilatory mechanism of this region comes from two studies by Tse et al, in which rats initially learned which flavour of food at a “start box” was associated with which location of similarly-flavoured food (Tse, Langston, Kakeyama, Bethus, Spooner, Wood, Witter & Morris, 2007; Tse, Takeuchi, Kakeyama, Kajii, Okuno, Tohya, Bito & Morris, 2011). Following training on six paired associates (PAs), the rats in these studies were presented with two new PAs. Note that the general nature of the task, stripped of specificity of a particular flavour or location, could be understood to be a “schema.” The association between flavour at the start box and flavour of food at a particular location composes a schema as it is a relationship between concepts, which can be extracted from multiple repetitions of the association using different details (i.e. specific flavours and locations). In the first study by Tse et al (2007), it was found that the new PAs were much more rapidly acquired than the original PAs (acquisition occurred in a single trial). Moreover, the new associations became hippocampal-independent much faster than had previously been shown, as reflected by a very brief retrograde amnesia gradient (48 hrs.), which the authors took to indicate that prior learning of the associated schema may have aided encoding, storage, or “consolidation” of the new PAs. In the second study by Tse et al (2011), it was discovered that the hippocampal-dependent learning of new PAs—the integration of new PAs into the existing schema—was associated with an up-regulation of immediate early genes in the prelimbic region of the medial prefrontal cortex, which is considered to be the rat’s analogue of the vmPFC, together with the infralimbic cortex (Vertes, 2004). Furthermore, it was found that pharmacological interventions targeted at this area prevented learning of the new PAs, as well as recall of the PAs constituting the original schema.
(Tse et al, 2011). Collectively, these studies provide evidence for the role of the vmPFC in assimilating new information into schemata.

Another indication of the implication of the vmPFC in integrating information into existing schemata comes from a study by Van Kesteren, Fernández, Norris & Hermans (2010). The researchers found that when new information is consistent with a strong prior schema, encoding involves less vmPFC activation and less hippocampal-vmPFC connectivity than when new information is to be integrated into a weak prior schema. Specifically, on the first day of testing, two groups of participants were shown the first part of a film, where these initially presented half-films constituted the “schemata” in this study. In one condition, the first half-film was shown in sequential order (strong prior schema), while in the other condition, it was shown in a mixed order (weak prior schema). On the following day, all participants were shown the second half of the film in sequential order, where this section of the film constituted the “new information.” The results of the study indicate that the vmPFC may play a role in assembling information into a schematic representation, as this region demonstrated greater activation when new information needed to be integrated into a weaker schema. Alternatively, one could interpret these results as reflecting inhibitory processes. For instance, it is possible that the participants viewing the mixed order half-film created a weak schema that later needed to be inhibited when new information was presented. It should be noted that narratives, such as the film presented in this study, constitute a grouping of associations between specific concepts, similarly to schemata; however, schemata, as defined earlier, are not synonymous with narratives, as they are typically generated through the repetition of narratives that retain similar relationships but differ in certain details. As such, the “schemata” referred to in this study (i.e. information presented in the first half of the film) do not precisely correspond to our earlier definition of schemata, but could more aptly be referred to as “narratives.”

While the studies just described emphasize that the vmPFC helps to assimilate information into schemata, here we present a paper suggesting an inhibitory role of this region. In a recent review on the topic, Nieuwenhuis and Takashima (2011) integrated findings from the consolidation literature with studies on vmPFC lesions in an attempt to explain the increase in vmPFC activity that is repeatedly shown to occur in conjunction with memory “consolidation.” Based on this review, it was concluded that the role of the vmPFC, specifically the subgenual vmPFC, may be to integrate information represented in separate areas of the limbic system, and subsequently
inhibit inappropriate representations in these areas. Nieuwenhuis and Takashima further hypothesized that the integrated representation in the subgenual vmPFC may replace some of the direct connectivity amongst the limbic areas over time.

In support of their proposal, Nieuwenhuis and Takashima (2011) first cited evidence from fear extinction literature (Peters, Kalivas & Quirk, 2009; Sotres-Bayon, Bush & LeDoux, 2004), which suggested that the vmPFC integrates amygdala-dependent CS-US memory and the competing CS-no-US memory, and subsequently inhibits the activity of limbic areas that is inappropriate in a particular situation. Next, the authors highlighted findings from valuation literature, which indicated that the vmPFC appears to integrate information from the limbic system, such as gains, losses, expected values, and reward magnitudes, in order to achieve valuation (Tom, Fox, Trepel & Poldrack, 2007). They also included evidence to suggest that the vmPFC suppresses the activity of the ventral striatum, which underlies value representations, supporting their idea that an integrated representation of information from the limbic system serves to suppress irrelevant representations in a given situation (Öngür & Price, 2000; Peters, Kalivas & Quirk, 2009). Nieuwenhuis & Takashima (2011) indicated that these results are in line with the finding that damage to the vmPFC may lead to increased risk taking, as this behaviour could be due to an impaired inhibition of the ventral striatum signaling reward expectancy.

Lastly, the authors introduced evidence from the confabulation literature: confabulations, which can occur with damage to the vmPFC, may be the result of impaired integration and suppression of limbic activity (Schacter, Norman & Koutstaal, 1998; Schnider, 2003; Schnider & Ptak, 1999).

Additional insight into the potentially inhibitory role of the vmPFC in representing schemata comes from literature on the cognitive mechanisms underlying schematic representation. While there is no mention in such literature of neurological correlates, it relates to the vmPFC when understood in conjunction with findings of a relationship between this region and schematic representation (see Kumaran, Summerfield, Hassabis, & Maguire, 2009; Tse et al., 2011; Van Kesteren, Fernández, Norris & Hermans, 2010). For instance, based on mathematical simulations, Cooper, Shallice, and Farringdon (1995) demonstrated that competition for activation amongst schemata is effected through a balance of lateral inhibition and self activation mechanisms, where self activation works in opposition to lateral inhibition. Note that “lateral inhibition” refers to when the retrieval of a concept in a well-established memory structure will
automatically inhibit related concepts (Blaxton & Neely, 1983; Johnson & Anderson, 2004). Cooper, Shallice, and Farringdon (1995) suggested that if a schema’s goal in influencing behaviour is not yet achieved—if it remains relevant—then it is subject to self activation, whereas once the schema’s goal has been achieved—when it is no longer relevant—then it becomes subject to lateral inhibition by competing schemata. According to this framework, highly active schemata inhibit their competitors more than moderately active schemata.

1.2 Confabulation and schematic representation

“Confabulation” is defined as the propensity to confuse untrue memories with true memories (Schnider, 2008). Specifically, confabulation is a memory disorder involving the production of false statements that are resistant to contradictory evidence (Gilboa & Verfaellie, 2010). An important feature of confabulation is that patients tend to exhibit anosognosia for their memory problem (Moscovitch, 1989).

Burgess and Shallice (1996) proposed that confabulation involves the intrusion of “input templates,” which they described as being strong generic memories that are not specific to any one event. By our definition, some of these “input templates” could be considered as schemata, while others could be considered as concepts, the basic units of schemata. Burgess and Shallice suggested that input templates are the “starting values” for the recollection process and that confabulators have difficulty “deactivating” these memories when inappropriate and moving on in their memory searches. Burgess and McNeil (1999) reported evidence of the operation of schemata in confabulation. Their patient, B. E., demonstrated highly stable confabulatory content that was restricted to one aspect of his life. Specifically, B. E. demonstrated a recurrent erroneous memory of having spoken with his business partner about work that needed to be done on a particular day, but his confabulatory content did not extend beyond such work-related events. Burgess and McNeill suggested that this memory is an example of an “input template,” as it is something that B. E. would have done many times in the past, and thus was not specific to any one occasion.

Also consistent with the proposal by Burgess and Shallice (1996) is the common observation that confabulations are most frequent in the autobiographical domain, as well as the finding that autobiographical confabulations are associated with the strongest confidence in their veracity (Gilboa, 2004; Gilboa, Alain, Stuss, Melo, Miller, & Moscovitch, 2006; Moscovitch, 1989). This
dominance of autobiographical memory in confabulation may be evidence of the influence of schematic representation on confabulation, as the self-schema is the richest and most complex human schematic representation and thus would be expected to be the most resilient to inhibition (Gilboa, 2004, 2010).

To summarize, the literature linking confabulation and schematic representation suggests that untrue memories may be associated with a failure to suppress strong, pre-existing general memory representations (i.e. schemata). However, the empirical evidence of the association between schemata and confabulation is scant and needs further probing. Neuroanatomically, it appears that the vmPFC may be critical in performing such suppression as a lesion to this brain region is sufficient to cause confabulation (Gilboa & Moscovitch, 2002).

In discussing the relationship between schemata and confabulation, it should be noted that schemata are not depicted as a plausible cause of confabulation, but rather appear to determine the content, and possibly the frequency of confabulations (Gilboa, 2010). With respect to the strategic retrieval framework of confabulation, the reliance on default schemata for retrieval is categorized as an “associated feature” of the confabulatory syndrome, to be distinguished from the “core features” of the syndrome: deficits in feeling of rightness monitoring, editor monitoring, and control processes (Gilboa, 2010).

1.3 Schematization in memory transformation

As previously mentioned the memory transformation hypothesis proposes that as memories become hippocampal-independent, they lose their contextual details and become schematized (Winocur & Moscovitch, 2011; Winocur, Moscovitch & Sekeres, 2007). This process is illustrated by a study by Winocur, Moscovitch and Sekeres (2007). In a rat experiment, context for memory retrieval was manipulated after a short delay (1 day) following training in a socially acquired food preference task or contextual fear conditioning task, and also after a long delay (28 days). It was found that rats demonstrated greater learned responses after a short delay if the context was the same as at encoding than if it was different; however, they performed equally across same and different contexts after the long delay. These results indicate that while the memory was context-dependent shortly after encoding, with time, the memory became context-independent. This finding is inconsistent with the standard consolidation theory which proposes that over time, memories are consolidated in such a manner as to retain their initial contextual
features (Squire, 1992; Squire & Alvarez, 1995). Furthermore, the results appear to indicate that memory becomes generalized over time, which is congruent with the transformation hypothesis.

A similar study by Wiltgen and Silva (2007) demonstrated that mice could discriminate between the training environment within which they acquired contextual fear memory and a novel environment for up to 14 days. However, with a greater passage of time (36 days), the fear memory no longer appeared to be context-specific as the mice demonstrated their conditioned fear response in both the training and novel environments. This increase of context-independence of memory with passage of time is synonymous with schematization of memory and thus congruent with the memory transformation hypothesis.

A last example of the implication of schematization in memory transformation comes from Conway (2009). In his study, participants listed as many specific memories as possible from several days immediately prior to testing. The results indicated a steady decline in the number of memories listed with increasing retention interval. It was also found that memories from three days prior or from even further back were described much more generally than memories from within the past three days. These descriptions of remote events were more generic and more concerned with routines and schemata than with specific events. The results support the idea that as memories age, certain specific episodic memories may be transformed into more generic representations, or schemata, as described in the memory transformation hypothesis.

1.4 Summary of literature review

The evidence presented above can be summarized in the following manner. Firstly, the vmPFC appears to play a role in schema-dependent memory processes. For example, in a rat study (Tse et al, 2011), it was found that the integration of new paired associates into a pre-existing schema was associated with an up-regulation of immediate early genes in the prelimbic region of the medial prefrontal cortex. Further evidence is provided by findings showing that activation of the vmPFC is greater when integrating information into a weak prior schema, as compared to a strong prior schema (van Kesteren, Fernández, Norris, & Hermans, 2010). Additionally, it has been proposed that the vmPFC may be responsible for inhibiting inappropriate schematic representations (Nieuwenhuis & Takashima, 2011).
Secondly, there appears to be a relationship between confabulation and schematic representation. This was outlined in the proposal by Burgess and Shallice (1996) that confabulation involves the intrusion of “input templates,” and exemplified in Burgess and McNeil’s (1999) case study of B.E (see also Moscovitch, 1989). The high frequency and confidence of confabulations of an autobiographical nature further support the influence of schematic representation on confabulation.

Lastly, evidence was outlined for the involvement of schematization in memory transformation. Two rodent experiments found that performance is context-specific after a short delay following training, but context-independent after a long delay (Wiltgen & Silva, 2007; Winocur, Moscovitch, & Sekeres, 2007). Further support for this hypothesis is provided by evidence that, with time, the general, routine-like nature of memory increases as memories become more remote (Conway, 2009).

1.5 Study rationale

By integrating the literature linking schemata to the vmPFC, confabulation, and memory transformation, it becomes apparent that there is strong evidence that schematic representation is supported by the vmPFC. Despite literature reviews hypothesizing the general role of this region, the mechanism for schematic representation remains unknown and needs empirical investigation. In order to test whether the vmPFC is responsible for activating relevant pre-existing schemata or inhibiting irrelevant ones, we designed a behavioural task that distinguishes these two abilities. Specifically, the task was designed to test whether the boundaries of a currently relevant schema would extend to include concepts recently activated as part of a currently irrelevant schema in patients with vmPFC lesions.

Behavioural performance on the task was measured in seven people, each of whom had damage to the vmPFC. Presence of confabulation was measured in each patient in order to test whether deficits in activating relevant schemata or in inhibiting irrelevant schemata are specific to individuals with damage resulting in confabulation or whether these deficits can arise in non-confabulating patients with vmPFC lesions. The measure of confabulation also served to confirm the hypothesized relationship between confabulation and errors in activating existing schemata.
Performance on the behavioural task was also compared across age, since it is known that in their memory for specific events and in source memory, older adults rely more heavily than do younger adults on semantic memory, and in particular on schemata (Koutstaal, Reddy, Jackson, Prince, Cendan, & Schacter, 2003; Mather & Johnson, 2003; McGillivray & Castel, 2010; Shi, Tang, & Liu, 2012). Older healthy adults, therefore, might perform differently from younger adults as some have associated the decision-making deficits in older adults as related to changes in the vmPFC (Bechara, Damasio, Tranel & Damasio, 1997; Bechara, Tranel, Damasio, & Damasio 1996; Denburg et al. 2007).
Chapter 2: Task

2.1 Procedure

A behavioural paradigm was created in order to differentiate one’s ability to activate a particular schema from one’s ability to inhibit a previously-relevant, but then irrelevant schema. There were three parts to the task.

In Part 1, participants were first asked to close their eyes for 30 seconds to imagine a given schema, either “a visit to the doctor,” or “going to bed at night.” This was done in order to ‘activate’ the schema. When the schema was “a visit to the doctor,” they were told: “Think about what it is like when you visit the doctor. Try to imagine the environment when you are there, the people you encounter, and the sequence of events that occur.” When the schema was “going to bed at night,” they were be told: “Think about what it is like when you go to bed at night. Try to imagine the sequence of events that occur when getting ready for bed and the environment when you are in bed.” Participants were next seated at a computer and told that they would see words appear on the monitor. They were asked to respond “yes” (left click) if the word that appeared on a given trial was associated with the schema they were just asked to imagine, and “no” (right click) if the word that appeared was not associated with that schema.

Words appeared in white in the centre of a black screen and were displayed until participants responded using the mouse. The next word appeared following a 500 millisecond inter-stimulus interval. Response accuracy and response latency were recorded across this part of the task. See Table 1 for the different types of stimuli presented in this part and their frequencies of presentation. Note that a prompt of the question they were asked to answer was displayed throughout the task so as to diminish the possible confound of participants forgetting the task instructions (e.g. “Is the following word closely associated with A VISIT TO THE DOCTOR?”). Similarly, prompts remained on the screen that indicated which mouse click (left or right) corresponded with a “yes” response and which corresponded with “no.” Following Part 1, there was a ten minute break prior to the administration of Part 2 of the task, during which non-linguistic neuropsychological tests were administered.
### Table 1

**Types of Task Stimuli**

<table>
<thead>
<tr>
<th>Part</th>
<th>Type of stimuli</th>
<th>Description</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>1</td>
<td>S1-R</td>
<td>concepts relevant to Schema 1(^a)</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>S1-I</td>
<td>concepts not relevant to Schemata 1 or 2</td>
<td>30</td>
</tr>
<tr>
<td>2 and 3</td>
<td>S2-R</td>
<td>concepts relevant to Schema 2(^b)</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>S1-R-PP</td>
<td>concepts relevant to Schema 1 presented in Part 1</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>S1-R-NP</td>
<td>concepts relevant to Schema 1 that were not presented in Part 1</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>S2-I(^c)</td>
<td>concepts not relevant to Schemata 1 or 2</td>
<td>30</td>
</tr>
</tbody>
</table>

\(^a\) Schema 1 refers to the schema presented in the question of Part 1

\(^b\) Schema 2 refers to the schema presented in the question of Parts 2 and 3

\(^c\) there was no overlap between schema-irrelevant concepts presented in Part 1 and those presented in Part 2.

Part 2 of the task progressed exactly as in Part 1, except that participants were told to imagine whichever schema had not been mentioned in Part 1. The behaviour required of the participants was the same as in Part 1, except that participants were required to indicate whether the words that appeared were associated with this new schema. The schema about which they were asked in Part 1 shall from here on be referred to as “Schema 1”, while the schema about which they were asked in Part 2 shall be referred to as “Schema 2”.

Part 3 immediately followed Part 2. In this part of the task, participants were presented with the same stimuli as in Part 2 and were this time asked to rate the degree to which each word was associated with Schema 2. Again, a prompt of the question was displayed throughout the task (e.g. “To what degree is the following word associated with GOING TO BED AT NIGHT?”). They were instructed to rate the association on a 4-point scale, where “1” represented a “high” association, while “4” represented a “weak” association. The value of “1” was selected to represent a “high” association as it is located to the left of the response pad, which corresponded well with a “left click” formerly representing “yes” to the question of association. See Table 1
for the different types of stimuli presented in Parts 1, 2, and 3 of the task and their frequencies of presentation.

2.2 Stimuli

The task for this study was created using E-Prime 1.2. The experimental stimuli consisted of two different types of words in Part 1 and four different types of words in Part 2 and 3 (see Table 1). The words were chosen based on a pilot study. Twenty-two participants completed a questionnaire in which they were asked to rate the degree to which 300 words were associated with the experience of “a visit to the doctor” on a scale of 1 to 4. On this scale, “1” pertained to “not at all related,” while “4” pertained to “highly related.” Also, as part of this pilot, these same participants rated the degree to which the same 300 words were associated with the experience of “going to bed at night” on the same scale. Note that 5 of the 22 participants only rated the associations of 200 of the 300 words. Also note that ratings on the second question (“going to bed at night”) of two participants were removed as their responses on words previously identified as associated with “sleep” and “bed” (Palermo & Jenkins, 1964) were low ratings, while responses on words previously identified as associated with “doctor” were high ratings. This finding suggests that on the second question, these participants continued to rate the association of words to the experience of “a visit to the doctor”, as opposed to the association to the experience of “going to bed at night”.

K-means clustering was used to divide the words presented in the pilot study into two clusters based on the ratings given to “a visit to the doctor.” The results were a doctor-relevant cluster consisting of 78 words, with a mean rating of 3.02 on the scale of 1 to 4, and a doctor-irrelevant cluster consisting of 222 words, with a mean rating of 1.40. K-means clustering was next used to divide the words presented in the pilot study into two clusters based on the ratings given to “going to bed at night.” The results were a bed-relevant cluster consisting of 70 words, with a mean rating of 3.11, and a bed-irrelevant cluster consisting of 230 words, with a mean rating of 1.23.

The mean distance of the ratings of words in the “doctor” cluster to the cluster centre was 0.392, with a standard deviation of 0.250. The mean distance of the ratings of words in the “bed” cluster to the cluster centre was 0.456, with a standard deviation of 0.240. The difference in mean distance of ratings of doctor-relevant words to the doctor cluster centre and the mean distance of
ratings of bed-relevant words to the bed cluster centre was not significant \( (p = 0.606) \). This indicates that the words in one schema were not more closely associated to each other than the words in the other schema.

A similar comparison was done using the words that were selected to be used in the behavioural task, rather than the entire set of words from the pilot. It was found that the mean distance of ratings of doctor-relevant words to the doctor cluster centre was 0.405, with a standard deviation of 0.265. The mean distance of ratings of bed-relevant words to the bed cluster centre was 0.421, with a standard deviation of 0.229. The mean distance of ratings of the doctor-relevant words chosen for the task to its cluster centre and the distance of ratings of the bed-relevant words chosen for the task to its cluster centre did not differ significantly \( (p = 0.869) \).

Lastly, the distances of the ratings of the schema-relevant words selected for use in the behavioural task to the cluster centre of the other schema was measured. It was found that the mean distance of doctor-relevant words to the bed cluster centre was 1.939, with a standard deviation of 0.151. The mean distance of the bed-relevant words to the doctor cluster centre was 1.666, with a standard deviation of 0.324. The difference between these distances was highly significant \( (p = 0.000) \). Therefore, it appears that the bed-relevant words were rated as being significantly more associated with the schema of “a visit to the doctor,” than the doctor-relevant words were rated as being associated to the schema of “going to bed at night” (See Figure 1). Due to this difference in association, it was necessary to vary the order of presentation of the schemata in the behavioural task administered to healthy adults.
Figure 1. Relationship between ratings of association of pilot words to each schema. Each data point represents a word whose association to each schema was rated. Red data points indicate words that were rated as being part of both schema clusters. The orange elipsis encapsulates words part of the “doctor” cluster that are near the “bed” cluster, but not included in it. The orange circle encapsulates words part of the “bed” cluster that are near the “doctor” cluster, but not included in it.
Chapter 3: Study 1

3.1 Methods

3.1.1 Participants

Forty-one healthy adults participated in this study. They were recruited through the healthy volunteer pools at the Rotman Research Institute and at the University of Toronto’s Department of Psychology. Exclusion criteria for healthy controls included any diagnosis of a neurological disorder, psychiatric disorder, or systemic disorder (e.g. diabetes, alcoholism). The participants were divided into two groups based on age. The group of younger adults (n = 20; 10 females, 10 males) ranged from 18 to 29 years, with a mean age of 22 years. The group of older adults (n = 21, 11 females, 10 males) ranged from 47 to 77 years, with a mean age of 59 years.

The predicted Full Scale Intelligence Quotient (FSIQ) ranged from 101 to 119 for younger adults, and from 97 to 118 for older adults. Participants performed within the normal range on a battery of neuropsychological tests (see Table 2) with the following exceptions. One young adult was found to be below the normal range (z = -3.19) on the delayed Rey Figure recall, and another young adult was found to take significantly longer than the normal range when performing the TMT A (z = 2.58).

Table 2

Results of Neuropsychological Tests Across Age

<table>
<thead>
<tr>
<th>Group</th>
<th>Rey Figure (raw score)</th>
<th>TMT (seconds)</th>
<th>Digit Span (raw score)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C. a</td>
<td>I.R. b</td>
<td>D.R. c</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Younger</td>
<td>35.15 (0.89)</td>
<td>26.85 (4.86)</td>
<td>27.53 (4.70)</td>
</tr>
<tr>
<td>Older</td>
<td>32.55 (3.15)</td>
<td>20.52 (6.74)</td>
<td>20.93 (5.89)</td>
</tr>
</tbody>
</table>

a Rey Figure copy sub-test (maximum score is 36)
b Rey Figure immediate recall sub-test (maximum score is 36)
c Rey Figure delayed recall sub-test (maximum score is 36)
d Digit Span forward
e Digit Span backward
f standard deviation
3.1.2 Experimental design and measures

3.1.2.1 Behavioural task

The study was set up as a mixed factorial design, with type of Stimuli as a within-subjects factor and Age as a between-subjects factor. The order of presentation of the schemata (i.e. which schema was presented in Part 1 and which schema was presented in Parts 2 and 3) was varied. As a result, 11 of the younger adults viewed the “bed” schema first (6 females, 5 males) and 9 of them viewed the “doctor” schema first (4 females, 5 males). Similarly, 10 of the older adults viewed the “bed” schema first (5 females, 5 males) and 11 of them viewed the “doctor” schema first (6 females, 5 males).

3.1.2.2 Neuropsychological tests

A battery of neuropsychological tests was administered, which included the Wechsler Test of Adult Reading as a measure of general intellectual ability (Wechsler, 2001), the Rey-Osterrieth Complex Figure Test (Rey Figure) as a measure of visuospatial memory (Osterrieth, 1944; Rey, 1941); the Trail Making Task (TMT) as a measure of executive function, specifically shifting abilities (Lezak, Howieson, & Loring, 2004); and Digit Span subtests of the WAIS-III as a measure of short-term memory and working memory (Wechsler, 1997). These tests served as confirmation of normal executive functioning ability and episodic memory capacity. Furthermore, the Rey Figure copy and immediate recall, as well as the TMT and Digit Span tests served as a distraction during the 10 minute break between Parts 1 and 2 of the behavioural task. The break was necessary so as to diminish the possibility of perseveration on Part 2 to Part 1 task instructions. However, it was also necessary that the neuropsychological tests employed during the break would not require the activation of semantic information, such as schemata, concepts, or categories.

3.2 Results

A mixed-ANOVA was performed with Age as the between-subjects factor and type of Stimuli as the within-subjects factor, examining reaction time in milliseconds (ms) as the dependent variable. For each participant, reaction times exceeding 2.5 standard deviations from the mean of that individual’s reaction times to words of a particular type of stimuli were treated as outlying scores and removed from analyses. There were between 0 and 2 outlying scores for each type of
stimuli for each participant. There was a main effect of Age (F(1,5) = 12.751, p = 0.001), indicating that older adults demonstrated longer reaction times than younger adults regardless of the type of stimuli (Figure 2). This finding is consistent with previous research demonstrating reaction time slowing with age (Der & Deary, 2006). There was also a main effect of Stimuli (F(1,5) = 13.800, p = 0.000) (see Figure 2).

**Figure 2.** Reaction time in classification of different types of stimuli as either schema-relevant or schema-irrelevant across age. Blue bars depict the mean reaction time of younger adults and red bars depict the mean reaction time of older adults. The error bars represent the standard error of the mean. The significant differences in reaction times to different types of stimuli, as indicated by the “*”, refer to overall differences, irrespective of age. “**” represents p < 0.05.

There was a significant interaction between Stimuli and Age (F(1,5) = 2.647, p = 0.024). As older adults took significantly longer than younger adults across all types of stimuli, the interaction was delineated by looking at the significance of the interaction between Stimuli and Age for different pairs of stimuli types. There was only a significant interaction with Age when comparing reaction time to S1-R-NP and S2-I words (F(1,1) = 4.901, p = 0.033) (see Figure 3).

**Figure 3.** Interaction between age and type of stimuli when comparing reaction time to S2-I and S1-R-NP words. The error bars represent the standard error of the mean.
Comparisons between reaction time in response to specific pairs of stimuli types were made using paired-samples t-tests. These revealed that regardless of age, participants took significantly longer to reject S1-I words than S2-I words, possibly indicating a practice effect ($t(40) = 2.936, p = 0.005$). It was also found that participants took significantly longer to reject S1-R-NP words than to reject S2-I words ($t(4) = 7.274, p = 0.000$), and also took longer to reject S1-R-PP words than S2-I words ($t(4) = 6.681, p = 0.000$). No other reaction time differences between pairs of stimuli types were significant ($p > 0.05$).

Another mixed-ANOVA was performed with Age as the between-subjects factor and type of Stimuli as the within-subjects factor, examining accuracy as the dependent variable. There was a significant main effect of Stimuli on accuracy ($F(1,5) = 19.214, p = 0.000$) (see Figure 4). There was no main effect of Age on accuracy and no interaction between Stimuli and Age ($p > 0.05$).

![Figure 4. Percent accuracy in different types of stimuli as either schema-relevant or schema-irrelevant. The error bars represent the standard error of the mean.](image-url)

A last mixed-ANOVA was performed with Age as the between-subjects factor and type of Stimuli as the within-subjects factor, examining ratings of association to Schema 2 as the dependent variable. The ratings, as would be expected, differed significantly across Stimuli ($F(1,3) = 1430.791, p = 0.000$). There was no main effect of Age ($p > 0.05$). There was a significant interaction between Stimuli and Age ($F(1,3) = 3.136, p = 0.037$), where a simple effects analysis revealed the following: that older adults rated S2-I stimuli as significantly less associated to Schema 2 than did younger adults ($F(1,1) = 6.024, p = 0.019$), and no significant difference across age in ratings of association of S2-R, S1-R-PP, or S1-R-NP stimuli ($p > 0.05$) (see Figure 5). The difference between ratings of association of S2-I stimuli across age is due to a ceiling effect and so this effect is also responsible for the observed interaction.
Figure 5. Mean ratings of association of different stimuli types to Schema 2 across age. Ratings of association were measured on a 4-point scale where “1” represents that a word is highly associated to Schema 2, while “4” would mean that a word is weakly associated to Schema 2. Blue bars depict the mean ratings of association of younger adults and red bars depict the mean reaction time of older adults. The error bars represent the standard error of the mean. “*” represents $p < 0.05$.

### 3.3 Discussion

Regardless of age, participants demonstrated greater response latencies when rejecting words pertaining to the previously relevant schema than words irrelevant to both schemata. Consequently, it is assumed that the previously relevant schematic representation needed to be inhibited in order to complete the new task presented in Part 2. It appears, however, that older adults required greater cognitive resources to exert inhibition on the prior, irrelevant schema, specifically for words they had not previously classified. This finding is reflected by the observed interaction between Age and type of Stimuli on reaction time, wherein the reaction time difference to S1-R-NP concepts and S1-I concepts was greater for older adults than for younger adults. There are two plausible explanations: 1) there was heightened activation of the previous schema in older adults, or 2) their inhibitory processes were compromised.

Both explanations imply that there was more persistent activation of the previously relevant schema in older adults. This persistent activation could be a precipitate of the greater reliance on existing schemata with age, as other memory processes become less reliable. This account is corroborated by previous studies indicating that older adults rely more heavily than do younger
adults on prior schematic representations when given the opportunity in their recall and recognition of specific events (Koutstaal, Reddy, Jackson, Prince, Cendan & Schacter, 2003; Mather & Johnson, 2003; McGillivray & Castel, 2010) and in source memory (Shi, Tang, & Liu, 2012). Older adults may also rely on schemata to a greater extent than younger adults in their formulation of expectations for a particular situation (Schutzwohl & Reisenzein, 1999). Where the two explanations differ is that the former explanation proposes this persistent activation as placing an increased demand on cognitive resources to inhibit the activation, while the latter explanation proposes that the persistent activation results from inefficient inhibition.

The first explanation, that there was heightened initial activation of Schema 1 in older adults, is in line with a proposal put forward by Cooper, Shallice, and Farringdon (1995) for how pertinent schemata are selected to guide actions. Part of their proposal entails that a schema remains selected even if its activation drops below the selection threshold, until the activation of one of its competitors rises above that of the selected schema. It is thus possible that in older adults, Schema 1 was brought to a higher activation than in younger adults, thus requiring yet greater activation of Schema 2 to properly compete and laterally inhibit Schema 1.

Recall that the alternative explanation for the findings is that the older adults had compromised inhibitory processes, leading them to require greater cognitive resources in order to inhibit responding to S1-R-NP words. This possibility is consistent with previous findings that older adults have impaired inhibitory control (Hasher, Stoltzfus, Zacks, & Rypma, 1991). However, this does not account for the increase in reaction time difference between responding to previous schema relevant concepts and to completely irrelevant concepts as based on this reasoning alone, one might expect older adults to have equal difficulty inhibiting all irrelevant concepts. To address this difference, one might speculate that the inhibition of concepts that are closely associated with each other (i.e. members of a schema) would require greater cognitive resources than isolated concepts. With each presentation of a concept that is part of the irrelevant schema, activation would propagate to other members of the same schema, bringing them closer to awareness (see semantic processing discussion by Collins & Loftus, 1975). If these primed concepts were presented later in the task, greater cognitive resources would then be required to inhibit them in contrast with novel concepts that have not been primed. Note that by this expanded explanation, one would assume that older adults would have also demonstrated a greater difference in response latencies to S1-R-PP and S2-I than younger adults; however, this
was not the case. The likely reason is that both S1-R-NP and S2-R concepts were novel concepts primed in the manner described above and both requiring a decision regarding relatedness to Schema 2. In contrast, S1-R-PP concepts were not novel and had already been rated as associated with Schema 1 during Part 1 of task.

A new experimental paradigm would need to be created in order to disentangle the two plausible explanations. For instance, they could have been distinguished had additional lures belonging to a new irrelevant schema been presented in Part 2 of the task. The task that was actually administered confounded the ability to inhibit an irrelevant schema with the effects of the previously activated schema.
Chapter 4: Study 2

4.1 Methods

4.1.1 Participants

4.1.1.1 Summary

Seven patients with lesions to the ventromedial prefrontal cortex (vmPFC) were tested. All patients acquired brain damage following rupture of an anterior communicating artery (ACoA). The patients were recruited from the Baycrest Hospital Psychology Department, the Rotman Research Institute’s patient registry, and the Toronto Rehabilitation Institute Acquired Brain Injury Neurorehabilitation Program.

Ten healthy controls were also tested, matched to the patients for age (within a five-year difference), sex, and years of education (within a one-year difference). Each patient matches two healthy adults in the control group. There was one exception, wherein one of the control participants meant to match P2 was six years older than him, rather than being within a five-year age difference. These healthy participants were recruited from the Rotman Research Institute’s healthy volunteer pool. Exclusion criteria for healthy controls included learning English after the age of six years and any diagnosis of neurological disorders, psychiatric disorders, or systemic disorders (e.g. diabetes, alcoholism).

4.1.1.2 Patient qualitative descriptions

P1 is a right-handed male, aged 43 years at the time of testing with 12 years of education. His occupation was as an electrician and his first language is English. His ACoA ruptured three months prior to testing, resulting in right hemisphere damage to the orbitofrontal cortex, inferior ventromedial prefrontal cortex, ventrolateral prefrontal cortex, inferior frontal pole, inferior medial paracingulate, and inferior medial cingulate. Based on his clinical file, reports from his spouse, and quantification based on the confabulation battery, it was determined that P1 had begun to confabulate immediately following his aneurysm and that he still demonstrated confabulation at the time of testing. His spouse reported that he had a tendency to act upon his confabulations. For example, while hospitalized, his spouse and he were going to go out for coffee and P1 insisted that he had parked a car in the lot and tried to find it. He claimed to have bought the car a few days before being admitted to the hospital and that he had not yet had a
chance to tell his wife about the car. In reality, he had not bought a car and had been taken to the hospital by ambulance.

P2 is a right-handed male, aged 39 years at the time of testing with 12 years of education. His occupation was as a bus driver and his first language is English. His ACoA ruptured a month and a half prior to testing. Damage to the following right hemispheric brain regions was evident: orbitofrontal cortex, inferior medial cingulate, head of the caudate nucleus, and hypothalamus. Based on his clinical file, reports from his spouse, and quantification based on the confabulation battery, it was determined that P2 had begun to confabulate immediately following his recent aneurysm and that he still demonstrated mild confabulation at the time of testing. His affect was labile at the time of testing, frequently fluctuating between laughing and crying.

P3 is a left-handed male, aged 43 years at the time of testing with 12 years of education. His occupation was as a production supervisor and his first language is English. His ACoA ruptured three years and three months prior to testing, resulting in bilateral damage to the orbitofrontal cortex, inferior ventromedial prefrontal cortex, inferior frontal pole, and inferior medial cingulate, as well as to the rostrum of the corpus callosum, anterior commissure, and right thalamus. He has been diagnosed with depression for which he was taking anti-depressant medication at the time of testing. P3 could not recall instances that had occurred a few minutes prior and thus repeatedly asked the experimenter for clarification as to where he was and what he was doing.

P4 is a right-handed female, aged 59 years at the time of testing with 13 years of education. Her occupation was most recently as a care provider, although she spent most of her career as a graphic artist. Her first language is English. Her ACoA ruptured a month and a half prior to testing. She had undergone previous aneurysms to the middle cerebral artery and posterior communicating artery a year prior. Damage was evident in the following regions of the right hemisphere: orbitofrontal cortex, inferior ventromedial prefrontal cortex, and inferior medial cingulate. Her sister described that since the aneurysm, P4 appeared to have difficulty creating new memories and did not seem to see how they have aged, talking frequently about friends from 40 years ago as though she had forgotten that time had passed.

P5 is a right-handed female, aged 61 years at the time of testing with 15 years of education. Her occupation was as a teacher and her first language is English. Her ACoA ruptured four years and
five months prior to testing, resulting in left hemisphere damage to the orbitofrontal cortex, ventrolateral prefrontal cortex, and inferior medial cingulate. Her spouse explained that P5 appears to have intact long-term memory, but will forget recent events, such as what she had eaten for breakfast earlier that day.

P6 is a right-handed female, aged 56 years at the time of testing with 15 years of education. Her occupation was as an executive director and her first language is English. Her ACoA ruptured 3 years and 10 months prior to testing, resulting in bilateral damage to the orbitofrontal cortex. P6 has been diagnosed with depression for which she was taking anti-depressant medication at the time of testing.

P7 is a right-handed female, aged 56 at the time of testing with 15 years of education. Her former career was in politics and her first language is English. Her ACoA ruptured 4 years and 9 months prior to testing, resulting in damage to the right orbitofrontal cortex and right inferior medial cingulate.

4.1.2 Experimental design and measures

4.1.2.1 Behavioural task

The study was set up as a case-series, comparing seven patients with overlapping damage to the ventromedial prefrontal cortex. Due to the small sample sizes, the order of schema presentation could not be varied across participants. All patients and control participants performed the task with the “bed” schema presented in Part 1 and the “doctor” schema presented in Parts 2 and 3. This order was selected as based on the data collected in Study 1, it was found that overall, accuracy in Part 2 of the task on the schema-1-relevant words was diminished in participants when the “bed” schema was presented first in comparison to when the “doctor” schema was presented first (F(1) = 16.962, p = 0.000), suggesting that this order of schema presentation may be more sensitive to prolonged activation of the first schema.

4.1.2.2 Neuropsychological tests

Both patients and control participants were administered the Wechsler Test of Adult Reading as a measure of premorbid general intellectual ability (Wechsler, 2001), the Rey-Osterrieth Complex Figure Test as a measure of visuospatial memory (Osterrieth, 1944; Rey, 1941); the
Trail Making Task (TMT) as a measure of executive function, specifically processing speed and shifting abilities (Lezak, Howieson, & Loring, 2004); and Digit Span subtests of the WAIS-III as a measure of short-term memory and working memory (Wechsler, 1997). As in Study 1, the Rey Figure copy and immediate recall, as well as the TMT and Digit Span, served as a distraction during the 10 minute break between Parts 1 and 2 of the behavioural task. The break was intended to diminish the possibility of perseveration on Part 2 of the task to Part 1 task instructions. These specific tasks were selected to be administered during this 10 minute interval as they do not require the activation of semantic information, such as schemata, concepts, or categories.

Additionally, the eight patients were administered a battery of the following neuropsychological tests after the behavioural task: the Stroop Colour-Word Test (Golden, 1978) as a measure of response inhibition; the California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan, & Ober, 1987) as a measure of episodic memory; and the Delis-Kaplan Executive Function System (D-KEFS) verbal fluency sub-test (Delis, Kaplan, & Kramer, 2001).

4.1.2.3 Anatomical neuroimaging

The patients’ lesions were verified with their clinical computed tomography (CT) scans or magnetic resonance imaging (MRI) scans. Specific frontal regions damaged in each patient have been identified by superimposing their individual scans on a brain template based on previously published guidelines (Stuss et al., 2002).

4.1.2.4 Confabulation battery

The patients’ history of confabulation was determined based on their clinical record and were also quantified through a modified Crovitz cue-word test (see Moscovitch & Melo, 1997 for description). This task was administered to all of the patients. The test measured the number of confabulations produced while participants answered a set of questions involving the retrieval of various types of semantic and episodic information. In summary, participants were first asked to clearly describe a personal event of which they were reminded when presented with each of 12 cue words. They were then asked to clearly describe a historical event that occurred before they were born of which they were reminded when presented with each of 12 additional cue words.
If the participant did not provide information or gave vague responses, then the cue word was repeated within a question. For example, if the word was “angry,” they might be asked “Can you remember a time when you or someone you know was angry?” If additional prompts were needed, broad questions were asked. These were either “Can you provide any other details?” or “Could you describe a specific event?” The broad nature of these questions differs from the means of administration described by Moscovitch and Melo (1997) and was implemented to minimize “provoked” confabulations on the one hand and maximize the probability of some response being provided. One measure of this task was the degree of detail reported by participants for a given memory (on a scale of 0 to 3), before and after prompting. The other measure was the confabulation score, where each incorrect detail was given a score of “1.”

For each response given by a patient to a particular cue word, a detail score was determined by averaging the two detail scores given by independent raters of the response. A rating of “0” was given if no event was specified, “1” was given if vague or general information about the event was provided, “2” was given if a description identifying the event was provided, supplying some detail but not including both time and location, and a rating of “3” was given if a detailed description was provided specifying both time and location.

Confabulation scores were also determined by assigning a score of “1” to each incorrect detail. Patient accounts of historical events were verified through the internet. If a patient’s account of an event was corroborated by a source on the internet, then it was concluded that the patient provided information that they themselves did not construct. Patient accounts of personal events were verified by contacting relatives or friends of each patient to verify the information provided in the patient’s account of personal events. If no friend or relative could verify a particular event, then the patients themselves were contacted a minimum of two weeks following testing and were prompted to re-describe a particular event. If the account was congruent with original information, then this was not deemed a confabulation, as spontaneous confabulations are not preserved over time (Kopelman, 2010). If the account was contradictory, then each contradictory detail given originally was deemed incorrect.
4.2 Results

4.2.1 Neuropsychological tests

4.2.2.1 Healthy adults

The scores of each participant on the Rey Figure test and Trail Making Test, and their forward and backward digit spans were converted into z-scores based on age and education-appropriate norms (Fastenau, Denburg, & Hufford, 1999; Tombaugh, 2004; Wechsler, 2008). The WTAR raw scores were converted to standard scores based on norms reported by Wechsler (2001), which were used to predict FSIQ.

The predicted FSIQ for this sample ranged between 106 and 118. All members of the control group were found to be within the normal range on all of the neuropsychological tests, with the exception of two individuals performing above average (z = 3.07 on TMT A; z > 3.00 on Rey Figure immediate and delayed recall) and one individual performing below average on the Rey Figure copying component (z = -3.33), but with recall within the normal range.

4.2.2.2 Patients

For the Rey Figure, the patients’ scores on each of the sub-tests were converted to z-scores based on age-appropriate norms reported by Fastenau, Denburg, and Hufford (1999). For the TMT, their scores on sub-test A and B were converted to z-scores based on age and years of education-appropriate norms reported by Tombaugh (2004). For Digit Span forward and backward, scores were converted to z-scores based on age-appropriate norms reported by Wechsler (2008). The WTAR raw scores of each patient were converted to standard scores based on norms reported by Wechsler (2001), which were then used to predict FSIQ. For the Stroop Colour-Word Test, raw scores were corrected for age differences using the formula described by Golden (1978), then an interference score was calculated and the corrected scores for each of the three sub-tests and for the measure of interference were converted to t-scores (mean = 50, standard deviation = 10), based on norms reported by Golden. For the verbal fluency sub-test of the D-KEFS, the number of words listed by each patient for “F,” “A,” and “S,” was summed to create a total “FAS” score, which was then subsequently compared to age-appropriate norms reported by Tombaugh, Kozak, and Rees (1999) to calculate the z-score for each patient on this test. Similarly, the number of words listed for “animals,” was compared to these norms to generate a z-score for this section of
the test. The patients’ CVLT raw scores were converted to standard scores based on norms recorded by Delis, Kramer, Kaplan and Ober (2000) for an indication of free immediate, short-delay, and long-delay recall, as well as an indication of cued short-delay and long-delay recall. Intrusions and repetitions were examined as well. Also, possible clustering techniques employed by the patients in order to learn the first list were investigated.

See Table 3 for full listing of scores of each patient on the neuropsychological battery, excluding the CVLT, for which sub-scores are presented in Table 4. Performance on any task that was found to be outside of the normal range is highlighted below.

Table 3

Patient Performance on Neuropsychological Tests

<table>
<thead>
<tr>
<th></th>
<th>Rey Figure</th>
<th>TMT</th>
<th>Digit Span</th>
<th>WTAR</th>
<th>Stroop</th>
<th>Verbal Fluency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C&lt;sup&gt;a&lt;/sup&gt;</td>
<td>I.R. &lt;sup&gt;b&lt;/sup&gt;</td>
<td>D. R. &lt;sup&gt;c&lt;/sup&gt;</td>
<td>A &lt;sup&gt;d&lt;/sup&gt;</td>
<td>B &lt;sup&gt;d&lt;/sup&gt;</td>
<td>F&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>P1</td>
<td>0.7</td>
<td>-0.71</td>
<td>-0.31</td>
<td><strong>3.61</strong></td>
<td><strong>6.25</strong></td>
<td>-1.29</td>
</tr>
<tr>
<td>P2</td>
<td>0.37</td>
<td>-2.06</td>
<td>-1.96</td>
<td>0.05</td>
<td>0.52</td>
<td>-0.57</td>
</tr>
<tr>
<td>P3</td>
<td>0.05</td>
<td><strong>-2.73</strong></td>
<td><strong>-2.64</strong></td>
<td>0.74</td>
<td>0.03</td>
<td>-0.57</td>
</tr>
<tr>
<td>P4</td>
<td>0.86</td>
<td>-1.16</td>
<td>-0.89</td>
<td>-1.16</td>
<td>-1.03</td>
<td>1.15</td>
</tr>
<tr>
<td>P5</td>
<td>-1.17</td>
<td>-1.46</td>
<td>-1.17</td>
<td>-1.05</td>
<td>-0.73</td>
<td>1.23</td>
</tr>
<tr>
<td>P6</td>
<td>0.63</td>
<td>1.31</td>
<td>1.24</td>
<td>-0.47</td>
<td>0.15</td>
<td>1.23</td>
</tr>
<tr>
<td>P7</td>
<td>0.95</td>
<td>-0.99</td>
<td>-0.97</td>
<td>-1.16</td>
<td>-1.13</td>
<td>-1.07</td>
</tr>
</tbody>
</table>

Note. Bolded values represent significant impairments.

<sup>a</sup> Rey Figure copy sub-test

<sup>b</sup> Rey Figure immediate recall sub-test

<sup>c</sup> Rey Figure delayed recall sub-test

<sup>d</sup> Digit Span forward

<sup>e</sup> Digit Span backward

<sup>f</sup> predicted Full Scale Intelligence Quotient based on Wechsler Test of Adult Reading score

P1 demonstrated significantly slow processing speed, as indicated by his performance on the TMT A and B. P2 and P3 demonstrated impaired visuospatial memory as indicated by their performance on the Rey Figure recall. Lastly, P5 demonstrated a superior verbal fluency reflected by her FAS score.
Table 4

*Patient CVLT Scores*

<table>
<thead>
<tr>
<th></th>
<th>List A immediate recall (T score)*</th>
<th>Short-delay free recall (T score)</th>
<th>Short-delay cued recall (T score)</th>
<th>Long-delay free recall (T score)</th>
<th>Long-delay cued recall (T score)</th>
<th>Total intrusions (T score)</th>
<th>Total repetitions (T score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>46</td>
<td>-1.5</td>
<td>-1.0</td>
<td>-1.0</td>
<td>-1.0</td>
<td>5.0</td>
<td>0.5</td>
</tr>
<tr>
<td>P2</td>
<td>27</td>
<td>-3.0</td>
<td>-3.0</td>
<td>-3.0</td>
<td>-2.5</td>
<td>1.0</td>
<td>-0.5</td>
</tr>
<tr>
<td>P3</td>
<td>23</td>
<td>-3.0</td>
<td>-4.0</td>
<td>-3.5</td>
<td>-3.5</td>
<td>2.5</td>
<td>-1.0</td>
</tr>
<tr>
<td>P4</td>
<td>25</td>
<td>-3.5</td>
<td>-4.0</td>
<td>-4.0</td>
<td>-3.5</td>
<td>1.5</td>
<td>-1.0</td>
</tr>
<tr>
<td>P5</td>
<td>34</td>
<td>-3.0</td>
<td>-3.5</td>
<td>-3.0</td>
<td>-3.5</td>
<td>2.5</td>
<td>0.0</td>
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<tr>
<td>P6</td>
<td>61</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>-1.0</td>
<td>-1.0</td>
</tr>
<tr>
<td>P7</td>
<td>22</td>
<td>-3.5</td>
<td>-2.5</td>
<td>-4.0</td>
<td>-3.5</td>
<td>1.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Note. Bold writing indicates significant impairments.

P2, P3, P4, P5, and P7 demonstrated significant episodic memory impairments as indicated by their performance on the CVLT. In addition, P1, P3, and P5 demonstrated a significantly high degree of intrusions on the task. The clustering techniques of the patients were investigated as well. Most of the patients employed these techniques to a degree that is within the normal range. P6, however, was above the normal range in her application of serial clustering forward (z = 4.50), serial clustering bidirectional (z = 5.00), and subjective clustering (z = 5.00). It can also be noted that while the learning slopes of P5 and P6 were within the normal range, those of P1 (slope = 0.40; z = -2.00), P2 (slope = 0.30; z = -2.00), P3 (slope = -0.40; z = -3.00), P4 (slope = 0.00; z = -2.5), and P7 (slope = 0.40; z = -3.50), were below the normal range.

4.2.2 Confabulation battery

The average detail scores for personal events and for historical events for each patient can be found in Table 5, with separate scores included for the response prior to prompting and the response including information provided after prompting. Cohen’s Kappa was computed as an estimate of inter-rater reliability for the detail scoring. Kappa was found to be 0.618 with a confidence interval of 0.555 to 0.681. According to Landis and Koch (1977), a Kappa value of 0.618 should be interpreted as “substantial agreement.” Table 5 also lists the total confabulation score of each patient as well as the number of cue words associated with responses including
incorrect details. See Appendix 1 for examples of responses given by the patients to the personal and historical cue words.

Table 5

**Patient Confabulation Battery Performance**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Personal Events</th>
<th></th>
<th>Historical Events</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prompt (#)</td>
<td>Rating b/f prompt (mean)</td>
<td>Rating a/f prompt (mean)</td>
<td>Total confab score</td>
</tr>
<tr>
<td>P2</td>
<td>3.00</td>
<td>0.42</td>
<td>3.33</td>
<td>5 [3]</td>
</tr>
<tr>
<td>P3</td>
<td>2.17</td>
<td>0.75</td>
<td>1.25</td>
<td>1 [1]</td>
</tr>
<tr>
<td>P4</td>
<td>1.50</td>
<td>1.25</td>
<td>1.54</td>
<td>0 [0]</td>
</tr>
<tr>
<td>P5</td>
<td>1.00</td>
<td>1.13</td>
<td>1.75</td>
<td>11 [3]</td>
</tr>
<tr>
<td>P6</td>
<td>0.67</td>
<td>1.67</td>
<td>2.08</td>
<td>0 [0]</td>
</tr>
<tr>
<td>P7</td>
<td>2.08</td>
<td>1.29</td>
<td>1.92</td>
<td>6 [3]</td>
</tr>
</tbody>
</table>

*mean number of prompts per cue word
bmean rating before first prompt is given
cmean rating after all prompts have been given
dtotal confabulation score. Square brackets enclose number of cue words that yielded incorrect details.

### 4.2.3 Behavioural task

#### 4.2.3.1 Accuracy

For each case, accuracy in responding to each type of stimulus was compared with that of the control group using a modified $t$-test described by Sokal and Rohlf (1995) which treats each individual case as a sample of $N = 1$. A modified $t$-test was selected rather than the standard method of converting the individual’s score to a $z$-score, as Crawford and Howell (1998) demonstrated that for a normative sample of less than 50, it is inappropriate to treat the mean and standard deviation of this sample as though they are parameters, which is required for the standard method. Note that raw accuracy scores for a given type of stimuli were converted into percent accuracy. Also, please see Table 1 for the number of words in each type of stimuli. It
should be noted that for S1-R-PP and S1-R-NP, there are only 15 words in each category of stimuli, whereas there are 30 words in each of the other categories. As a result, an error made in response to a word belonging to either of these two stimuli categories will more greatly affect percent accuracy than one error made in response to a word belonging to the other categories.

P2, P4, P5, and P7 did not differ significantly from control participants in accuracy in response to any of the types of stimuli ($p > 0.05$). For P1, accuracy was significantly worse than that of control participants when responding to S1-I ($t(9) = -34.328, p = 0.000$), S2-R ($t(9) = -3.814, p = 0.001$), S2-I ($t(9) = -22.883, p = 0.000$), and S1-R-NP ($t(9) = -4.421, p = 0.002$) stimuli. His accuracy did not differ significantly from controls when responding to S1-R or S1-R-PP stimuli ($p > 0.05$). P3 demonstrated significantly worse accuracy than did controls on S1-I stimuli ($t(9) = -8.581, p = 0.000$), but did not differ significantly from controls in accuracy in responding to any of the other types of stimuli. This difference may have arisen due to a ceiling effect as P3 made 3 errors in response to this type of stimuli, out of a possible 30, while the mean accuracy of the control group was 0.99 with a standard deviation of 0.01. P6 also demonstrated significantly poorer accuracy than did control participants on S1-R ($t(9) = -7.866, p = 0.000$) and S1-I stimuli ($t(9) = -34.328, p = 0.000$), but did not differ from control participants in accuracy in responding to the other types of stimuli ($p > 0.05$). This may be a reflection of an initial misunderstanding of the task instructions. It is also possible that her schema for “going to bed at night”, the first schema presented, differs significantly from that of the control participants, as she both included irrelevant words in this schema and excluded relevant words. See Figure 6 for a representation of the percent accuracy of each case in comparison to the control group for each type of stimuli.
Figure 6. Comparison of patient and control group percent accuracy in responding to each type of stimuli. "*" represents accuracy scores of a patient that are significantly different from those of the control group ($p < 0.05$).
4.2.3.2 Reaction time

For all participants, reaction times to particular words were removed from analysis if they exceeded 2.5 standard deviations above the mean reaction time for that particular type of stimuli for that individual. Number of reaction time outliers for a given type of stimuli for a given participant ranged between 0 and 2. For each patient, the differences in reaction time in response to the various types of stimuli were compared to the mean differences in reaction time observed in the control group. It was important not to directly compare a patient’s reaction time to a specific type of stimuli to the mean reaction time to that type of stimuli of the control group, as this would not take into account the individual differences in general reaction time. For example, the finding that a particular patient is consistently slower at responding to any type of stimuli could be due to a variety of factors and is thus difficult to interpret. It was necessary to include a relevant personal baseline response time in order to isolate whether damage to the vmPFC or demonstration of confabulation was associated with differential responding to schema-relevant, schema-irrelevant, or previous-schema-relevant stimuli.

The comparisons between reaction time measures within a specific case were conducted using the Revised Standardized Difference Test (RSDT) by Crawford and Garthwaite (2005). The RSDT tests whether the standardized difference between a patient’s score on one measure and their score on another measure is significantly different from the difference between these measures in controls. Differences in reaction time were compared between the following pairs of stimuli types: S1-R and S2-R; S1-I and S2-I, S2-I and S1-R-PP, S2-I and S1-R-NP, and S1-R-PP and S1-R-NP. See Table 6 for rationale of each contrast.

Table 6

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1-R and S2-R</td>
<td>comparison of activation of the two schemata</td>
</tr>
<tr>
<td>S1-I and S2-I</td>
<td>comparison of exclusion of irrelevant concepts from each of the two schemata</td>
</tr>
<tr>
<td>S2-I and S1-R-PP</td>
<td>exclusion of Schema 1 relevant items previously seen in comparison to baseline exclusion of completely irrelevant items</td>
</tr>
<tr>
<td>S2-I and S1-R-NP</td>
<td>exclusion of Schema 1 relevant items not previously seen in comparison to baseline exclusion of completely irrelevant items</td>
</tr>
<tr>
<td>S1-R-PP and S1-R-NP</td>
<td>exclusion of Schema 1 relevant items seen in comparison to exclusion of those not seen</td>
</tr>
</tbody>
</table>
For P1, P3, P4, P5, P6, and P7, there were no significant differences between the reaction time differences that each demonstrated between the various types of stimuli and those demonstrated by the control group ($p > 0.05$). For P2, the degree to which his reaction time to S1-R-NP stimuli was greater than that to S1-R-PP was significantly greater than the difference in reaction time seen in the control group ($p = 0.000$) (See Figure 7). He also differed significantly from control participants ($p = 0.039$) when comparing his reaction time to S1-R-PP stimuli with S2-I stimuli, wherein both he and the control group took significantly longer to respond to the former type of stimuli than the latter but that this difference was greatly exaggerated in P2. He similarly differed from control participants when comparing reaction time to S1-R-PP stimuli to S2-I stimuli ($p = 0.000$). The difference in reaction time between S1-R and S2-R stimuli, and also the difference in reaction time between S1-I and S2-I stimuli, did not differ significantly between P2 and the control group ($p > 0.05$).

![Figure 7. P2 reaction time in responding to different stimuli types. Error bars represent the standard error of the mean of the control group. “*” represents difference between reaction time to different types of stimuli that were significantly greater for the patient than for the control group ($p < 0.05$).](image)

For each patient, reaction time on items to which they responded “yes,” meaning that a given word is included in the schema in question, was compared to the reaction time on items to which they responded “no,” regardless of whether these responses were correct or incorrect. This analysis was performed for all responses of Part 1 together and then for all responses of Part 2
together. The reaction time differences observed in patients were each compared to that observed in the control group using the RSDT.

On Part 1, P1 took significantly longer to reject words (response of “no”) than to accept words as part of the schema in question (response of “yes”) in comparison to the control group ($p = 0.001$). In Part 2, when lures included words relevant to Schema 1, as well as those irrelevant to both schemata, the difference in reaction time between P1’s “yes” responses and his “no” responses was significantly smaller than was demonstrated by the control group ($p = 0.017$). On Part 1, P2 took significantly longer to accept words than to reject them in comparison to the control group ($p = 0.000$), while on Part 2, the opposite was true ($p = 0.001$). He also took significantly longer to accept words in Part 1 than he took to accept words in Part 2 in comparison to the control group ($p = 0.011$), and took significantly longer to reject words in Part 2 than he did to reject words in Part 1 ($p = 0.000$). None of the other patients differed from the control group in terms of the difference in reaction time to accept words as part of a schema and reaction time to reject words from being included in a schema.

### 4.2.3.3 Ratings of association

For each case, the average rating of association for each type of stimuli presented in Part 2 was compared with that of the control group using the modified $t$-test described by Sokal and Rohlf (1995). P1 rated S2-I ($t(9) = -85.812, p = 0.000$), S1-R-PP ($t(9) = -3.985, p = 0.003$), and S1-R-NP ($t(9) = -3.496, p = 0.000$) words as significantly more associated to Schema 2, the “doctor” schema, than did healthy controls. He did not differ significantly from controls in his rating of association of S2-R words to this schema ($p > 0.05$). P5 indicated a significantly greater rating of association of S2-I words to the “doctor” schema than did control participants ($t(9) = -9.535, p = 0.000$); however, it should be noted that she classified all S2-I words as highly unrelated to the schema (a rating of “4”) save for one word. Giving this one word a rating other than “4” yielded a significant difference between P5’s ratings and that of the control participants, as the mean rating for S2-I words for control participants was 4.00 with a standard deviation of 0.00. P5 did not differ from the control group in her ratings of association to any of the other stimuli ($p > 0.05$). P3 also rated S2-I words as significantly more associated to the “doctor” schema than did healthy participants ($t(9) = -38.139, p = 0.000$). P2, P4, P6, and P7 did not differ from the control group on their ratings of association of the various types of stimuli to the “doctor” schema. See
Figure 8 for a visual representation of the mean ratings of association of each case to each type of stimuli in comparison to the control group.

*Figure 8.* Patient ratings of association of different stimuli types to Schema 2. Ratings of association were measured on a 4-point scale where “1” represents that a word is highly associated to Schema 2, while “4” represents that a word is weakly associated to Schema 2. “*” represents ratings of a patient that are significantly different from those of the control group \((p < 0.05)\).
4.2.4 Lesion analysis

Damage to specific frontal regions was identified in each patient (see Figure 9) by superimposing their individual neuroanatomical scans on a brain template based on previously published guidelines (Stuss et al., 2002). See Figure 10 for an indication of the lesion overlap of P1 and P2, the patients who demonstrated significant impairment on the behavioural task, as well as a separate indication of the lesion overlap of the remaining patients. When the cumulative lesions of the remaining participants was subtracted from the cumulative lesions of P1 and P2, there was found to be a small sub-region of the vmPFC that was damaged in both P1 and P2 but in none of the other patients. That area involved the sub-callosal cingulate cortex (BA24/BA25), which has previously been hypothesized to be critical for production of confabulation (Schnider, 2003). Interestingly, this is the specific region within the vmPFC that Nieuwenhuis and Takashima (2011) hypothesized to be implicated in suppressing irrelevant representations in the limbic system. In their review, they referred to this area as the “subgenual vmPFC”.
Figure 9. Patient brain lesions.
Figure 10. Overlapping patient brain lesions. A) Lesion overlap of P1 and P2, patients with poor inhibition of previously-relevant schema, as indicated by accuracy and/or reaction time measures on task. Purple indicates regions damaged in only one patient, while red indicates overlap between patients. B) Lesion overlap of P3, P4, P5, P6, and P7, patients behaving similarly to control participants. C) Comparison between lesions of P1 and P2 (A) and lesions of the other patients (B). The colour bar indicates percentage of individuals with lesions to a given area who belong to group (A), meaning that the middle purple percentage bar designates regions where there is an identical percent of A and B. Furthermore, the yellow percentage bar designates regions common to both P1 and P2 that are not common to any of the other patients.
4.3 Discussion

The diverse functions supported by the ventromedial prefrontal cortex (vmPFC) appear to indicate that this region has a dynamic role in employing existing schemata to help predict outcomes and guide behaviour in a given context (Kroes & Fernández, 2012; Roy, Shohamy, & Wager, 2012). Previous studies have demonstrated that the vmPFC plays a role in assimilating new information into existing schemata (Takeuchi, Kakeyama, Kajii, Okuno, Tohyama, Bito & Morris, 2011; Van Kesteren, Fernández, Norris & Hermans, 2010), in predicting outcomes and in decision-making (Bechara, Damasio, Tranel & Damasio, 1997; Bechara, Tranel, Damasio, & Damasio 1996). However, the mechanism for representing the appropriate schema in a particular situation was hitherto unknown, although some had hypothesized that it is an inhibitory one (Burgess & Shallice, 1996; Nieuwenhuis & Takashima, 2011). As such, this study sought to characterize the involvement of the vmPFC in representing schemata. Specifically, it was designed to test whether the vmPFC is responsible for activating relevant schemata or inhibiting irrelevant ones.

The results indicate that not all vmPFC damage affects the ability to identify whether or not a concept is part of a given schema. The presence or history of confabulation, however, appears to be associated with dysfunction in this respect. For instance, P1 differed significantly from the control group in his accuracy on the task (see Figure 6) and P2 differed significantly from the control group in his response latencies on the task (see Figure 7). These were the only two patients who had been described by family members as producing spontaneous confabulatory content—P1 was reported to have continued to do so since his aneurysm, whereas P2 was reported by his spouse as only having done so within the week following his aneurysm. At testing, P1 stated 39 erroneous details during the confabulation battery, while P2 stated only 8. As the performance of the patients with confabulation differed from the control group, but the performance of the other patients with vmPFC lesions did not, it is possible that a sub-region of the vmPFC is implicated in the representation of schemata, which, when damaged, affects this cognitive function and subsequently results in confabulatory accounts. Figure 10 identifies a plausible contender for such a sub-region, as there is an area within the vmPFC—the sub-callosal cingulate cortex—that was damaged in both P1 and P2, but in none of the other patients. Furthermore, this is the sub-region that Nieuwenhuis and Takashima (2011) proposed to be
implicated in the suppression of irrelevant information in the limbic system and it has also previously been hypothesized to be critical for production of confabulation (Schnider, 2003).

To evaluate whether the vmPFC—or this sub-region of the vmPFC—is responsible for activating relevant schemata or inhibiting irrelevant schemata, it seems necessary to examine the performance of P1 and P2. On that note, the erroneous schema representations evident in the patients with spontaneous confabulation could be indicative of 1) nebulous schemata, or 2) deficient semantic lateral inhibition. The case for each possibility is presented below.

4.3.1 Nebulous schemata explanation

As P1 demonstrated significantly poorer accuracy than the control group both in properly indicating that concepts are part of a schema (S2-R) and in properly indicating that concepts are not part of a schema (S1-I, S2-I, and S1-R-NP), it appears that the boundaries of his schemata are not clearly delineated. P2’s performance on the task can also be interpreted as demonstrating nebulous schematic representations. For instance, P2 spent more time than did control participants when deciding to properly reject words pertaining to an irrelevant schema in Part 2 (S1-R-PP and S1-R-NP) in comparison to properly rejecting words irrelevant to both schemata (S2-I) (See Figure 7). In addition, when not confounded by the presence of previous schema lures in Part 1, P2 took far longer than did control participants to give a “yes” response to indicate concepts as being part of Schema 1 in comparison to giving a “no” response to reject their inclusion. The results suggest that P2 may have found it difficult to determine whether or not a concept was part of the schema, regardless of the nature of the concept.

4.3.2 Deficient semantic lateral inhibition explanation

As indicated above, P1 demonstrated some difficulty in properly accepting concepts relevant to Schema 2, as reflected by his poor accuracy on S2-R items. The deficient semantic lateral inhibition explanation is based on the interpretation that P1 demonstrated an inhibitory deficit that was more prominent than this formerly described difficulty. This interpretation stems from his poor accuracy in rejecting schema-irrelevant concepts in both parts of the task and in rejecting novel Schema 1-relevant lures, while he only demonstrated poor accuracy in properly accepting words into one of the schemata (Schema 1). It is also based on the finding that P1 took significantly longer to give a “no” response to reject words as being part of Schema 1 than to
give a “yes” response to accept them in comparison to the response latency difference of the control group. Note that this reaction time comparison included words that were erroneously classified. This significantly greater reaction time difference was not observed in Part 2 likely due to the large proportion of errors made by P1 in Part 2 (i.e. he may have spent an abnormally long time responding to a schema-irrelevant word, ultimately to erroneously select it as being part of the schema, thus lengthening the mean response time to accept words and rendering it more similar to his mean response time to reject them).

By this inhibitory account of the role of the vmPFC, one might attribute P1’s difficulty accepting relevant words into an appropriate schema to his frontal pole damage. Moscovitch and Winocur (2002) proposed that the frontal pole may work in conjunction with the vmPFC to set context-dependent criteria of felt-rightness for the correct acceptance of retrieved information (mediated by the frontal pole) and for the correct rejection of retrieved information (mediated by the vmPFC). Were these assertions to be true, one would logically hypothesize that damage to the vmPFC would result in dysfunctional rejection of incorrectly retrieved information; in other words, vmPFC damage would yield acceptance of incorrectly retrieved information. Also by this reasoning, acceptance of correct information would not be affected by a lesion to the vmPFC, but rather by a lesion to the frontal pole.

The deficient semantic lateral inhibition explanation can also account for P2’s performance on the task. Specifically, it could easily explain P2’s massive reaction time differences between responses to Schema 1-relevant lures and schema-irrelevant lures in Part 2. These magnified differences could reflect reduced efficiency in inhibiting responding to the previous schema lures in comparison to healthy adults. P2’s long response latencies to properly accept concepts as part of Schema 1 would be interpreted as being due to overly cautious control processes compensating for deficient feelings of rightness, which are said to comprise the confabulatory syndrome (Gilboa, Alain, Stuss, Melo, Miller, & Moscovitch, 2006). In Part 2, there was observed to be an opposite difference in mean response latencies between accepting and rejecting concepts as being schema-relevant, which can be attributed to his extremely long response latencies when rejecting lures pertaining to Schema 1. Based on the depiction of the confabulatory syndrome by Gilboa et al. (2006), these control processes may also be responsible for P2’s diminished production of confabulatory content at testing in comparison to the days immediately following his aneurysm.
4.3.2.1 Mechanism

Based on the cases described above, it seems that the mechanism underlying confabulation may be a lateral inhibition deficit in the semantic network. Recall that “lateral inhibition” refers to when the retrieval of a concept in a well-established memory structure will automatically inhibit related concepts (Blaxton & Neely, 1983; Johnson & Anderson, 2004). With successive retrievals from the same semantic category, there was previously found to be cumulating retrieval inhibition, as reflected by a linear increase in retrieval latencies and a linear decrease in response probability on a cued-retrieval task (Brown, 1981). Walley and McLeod (1988) described this process as an automatic spreading activation that, if strong enough to cause neurons to discharge, produces inhibitory effects through the mechanism of recurrent lateral inhibition. In addition, as previously mentioned, Cooper, Shallice, and Farringdon (1995) applied the notion of lateral inhibition to schemata.

Let us interpret the results of P1 as an example of the proposed semantic lateral inhibition deficit, given that P1 was the patient demonstrating florid spontaneous confabulation at testing. P1’s poor accuracy in rejecting schema-irrelevant concepts may be explained as the activation of relevant concepts continuing to propagate along pathways of associated concepts towards those that, when isolated, appear quite unrelated to the schema in question in healthy adults. In healthy adults, concepts associated with schema-relevant concepts, but not part of the schema itself, would be subject to lateral inhibition. Similarly, a competing schema may also be inhibited by this mechanism, as proposed by Cooper, Shallice, and Farringdon (1995), which is evident in healthy participants of this study through their high accuracy in responding to S1-R-PP and S1-R-NP stimuli in conjunction with their elevated response latencies to these items. P1, however, does not appear to have demonstrated lateral inhibition of the previously activated schema—but possibly continued self activation—based on his poor accuracy in responding to these same stimuli. See Figure 11 for a representation of the proposed model of activation in confabulating patients.
Figure 11. Proposed semantic lateral inhibition model of confabulation. Black circles represent concepts in Schema A, grey circles represent concepts in Schema B, and white circles represent concepts that are not part of either schema. Grey lines indicate associations between concepts. Black dashed lines indicate associations that should be inhibited in healthy adults when Schema A is activated in order to mitigate the degree of activation spreading along those associations to the related concepts that are not included in Schema A.

Note that this deficient lateral inhibition mechanism of confabulation is supported by the proposal by Burgess and Shallice (1996) that confabulating patients have difficulty deactivating inappropriate strong, generic memories (similar to our “schemata”) during recollection in order to continue in their memory search. Their proposal had been corroborated by qualitative case studies of individuals with confabulation, such as that of B. E. by Burgess and McNeill (1999); however, it had not yet been tested quantitatively.

For future studies, in order to directly test the hypothesized deficient lateral inhibition in confabulating patients, one could administer a lexical decision task where target words are preceded by words varying in degree of association to the target. Were the hypothesis correct, one would expect a heightened reflection of mediated priming in the response latencies to the target words in confabulating patients. In other words, it would be anticipated that words distantly related to the target word would be more likely to prime the target word—as measured by a diminished reaction time to the target—in confabulating patients than in healthy adults.

4.3.3 Unified explanation

It is possible that the erroneous representation of schemata in confabulating patients be accounted for by both explanations in conjunction. Schnider (2002) suggested that in healthy individuals, the suppression of currently irrelevant memories might be exerted by desynchronizing the synchronous activity of neuronal populations that represent activated
memories. It was specified that the desynchronization of cortical neural networks is induced by the posterior medial orbitofrontal cortex, which is part of the vmPFC. As a result, if the patient’s initial schemata were nebulous, then this may subsequently render it more difficult for these patients to properly desynchronize activity and appropriately inhibit irrelevant concepts.

4.3.4 Implications for the role of the vmPFC

This study confirms the involvement of the vmPFC in representing schemata and indicates that this function may be mediated specifically by the sub-callosal cingulate cortex. In patients with damage to this sub-region, the dysfunctional rejection of irrelevant concepts was much more severe than the dysfunctional acceptance of relevant concepts. Were this region responsible for activating relevant schemata, one would expect there to have been equally poor performance across all stimuli on the task. Therefore, while these findings do not necessarily confirm a strictly inhibitory role of the vmPFC, they do refute its role as purely serving to activate relevant schemata.

4.3.5 Additional insights

An additional insight from the current study is the apparent dissociation between confabulation and amnesia, given that P1 demonstrated florid confabulation, but was within the normal range on all episodic memory measures. Schnider (1996) identified that provoked confabulation and spontaneous confabulation are independent of one another, resulting from different mechanisms. It is evident that provoked confabulation arises from searching for information that is inaccessible to retrieval due to memory deficits (Kopelman 1987; Schnider, 1996). In contrast, spontaneous confabulation has been hypothesized as comprising executive functioning deficits super-imposed on memory impairment (Kopelman, 1987; Moscovitch, 1989), but the necessary implication of these proposed components had not been confirmed. The current study should serve to redirect investigations into the source of spontaneous confabulation away from testing hypotheses involving episodic memory impairment.

Furthermore, support for the memory transformation hypothesis is provided by a dissociation between spontaneous confabulation and amnesia. Specifically, the former disorder appears to be reliant on impaired schematic representation and may arise from damage to the vmPFC (Gilboa
& Moscovitch, 2002), while the latter involves impaired episodic memory and arises from damage to the hippocampus (Winocur & Moscovitch, 2011).

Lastly, if one were to apply the model of vmPFC function described above to the results of Study 1, the following would still remain unclear: did older adults require greater cognitive resources to inhibit previous schema lures because of 1) heightened activation of the previous schema initially, or 2) compromised inhibitory processes? This ambiguity remains because there was no functional or structural neuroanatomical component to this study. However, were one to interpret the results in terms of the second explanation—specifically that there is an inefficient semantic lateral inhibition mechanism in older adults—this could account for the greater reliance of older adults on schemata in their retrieval of memory for specific events. If older adults have inefficient semantic lateral inhibition, then when presented with a retrieval cue for the memory of a specific event, they would exert less lateral inhibition on a schema that is closely associated with this cue. As a result, the schema may provide additional cues for the memory search and possibly play a larger role in reconstructing the event at retrieval.
Chapter 5 : Conclusion

Collectively, these studies provide insight into the cognitive processes required when representing a relevant schema and allude to a possible neurological mechanism. All healthy adults, regardless of age, required inhibition of concepts associated with a previously-relevant schema when identifying relatedness to a currently relevant schema. Older adults appeared to require greater cognitive resources in order to inhibit lures pertaining to a previously relevant schema, possibly due to heightened activation of the previous schema initially, or to compromised inhibitory processes.

While not all damage to the ventromedial prefrontal cortex impairs the inhibitory process required by the task, individuals both with damage to the ventromedial prefrontal cortex and with either current or historical demonstration of confabulation were dysfunctional in this respect. It is thus plausible that damage to a sub-region of the vmPFC may be responsible for a deficit in semantic lateral inhibition, subsequently precipitating spontaneous confabulation. Evidence from this and previous studies suggests the sub-callosal cingulate cortex as the aforementioned sub-region. It is also plausible that this sub-region may be implicated in representing the structure of schemata, wherein damage to this region results in nebulous schematic representations. These two proposed functions may be interdependent and thus both accounts may be correct. While these findings do not necessarily confirm an inhibitory role of the vmPFC in its representation of schemata, they do refute its role as purely serving to activate relevant schemata.

The results of the second study may also serve to resolve the dispute as to whether spontaneous confabulation is necessarily superimposed upon episodic memory impairment (see Kopelman, 1987). It appears this is not the case, as one of the patients of this study demonstrated florid spontaneous confabulations, yet had no episodic memory impairment, as indicated by neuropsychological assessment. Lastly, the study provides empirical evidence of the relationship between spontaneous confabulation and schematic representation, which had hitherto only been demonstrated by qualitative descriptions of the nature of confabulatory content (Burgess & McNeil, 1999).
References


Appendix 1

Examples of Responses Given in Confabulation Battery

Responses to personal cue words:

**Angry**
This makes me think of when I was extremely young, probably pre-kindergarten. I was having a fight with a neighborhood boy. He was on one side of the fence and I was on the other. He used a swear word and I said it back when my mom was coming out and I remember her grabbing my arm and taking me into the house. My only reason for being upset was that she had done it in front of the boy. I wasn’t upset about having said it or being punished. I was upset because I was embarrassed. (Patient P4)

**River**
I have a memory of being on a river, but I don’t know what it’s called. I had two friends, who were a couple, and another friend who had come from Calgary. We were going to go visit these friends who’d rented a cottage. It was up North and very beautiful. They wanted to take us on a canoe ride on the river. At one point, we canoed through some kind of sewer thing… some round tube that was hard to get through. When we got through to the other side, we were in the middle of… where everything had been cut out in the middle of this sort of mini canyon. It was the only time in my life, where I’d say I had a spiritual experience. I was just filled with the beauty of the river, of the rocks, of the sky. I couldn’t talk. At one point, one of the women asked me if I was okay. They said I was overwhelmed. (Patient P6)

**Dog**
When I was younger, we had a dog named Teddy. He was black and white. My husband and I both grew up with dogs as children. When we had a family, we adopted a dog from the humane society. That wasn’t good because there was a reason they didn’t want him. We took him for a weekend to try him. He was already named: Biff. He chewed up all the grass and wouldn’t stay on the leash. We went to a family event and were back two hours later and he had chewed up all the baseboards, so we knew he wouldn’t work for the family. We took the dog back to the humane society and there were lots of tears. (Patient P7)
Responses to historical cue words:

**Miracle**
Well the way they discovered penicillin with moldy cheese. Everyone was dying of the common cold and the flu and then someone made someone a sandwich with a piece of moldy cheese and all of a sudden he felt better. They checked it out and did some kind of diagnostics and realized that it was good for curing colds. They then started molding cheese out on a high level and breaking it down to a way that they could make powder with and later a pill. They cured the common cold, the plague, the flu. Before that miracle, people were dying of the common cold. (Patient P1)

**Sea/Ocean**
I think of fishing. The Titanic. It sunk. It was a cruise ship that sunk. It hit an iceberg. A lot of people died. Many lives lost. This happened a long time ago… not sure where it was. (Patient P2)

**Assassination**
Abraham Lincoln was assassinated. He was at a theatre watching a play. He was in the balcony sitting with someone. He was shot by a man named Booth. That’s my first thought. He was at a play and he was in the balcony and the man shot him. I think his wife may have been there. Her name was Mary Todd. (Patient P5)