The well-worn route revisited: Striatal and hippocampal system contributions to route learning in human navigation

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Material Abstract

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Parallel spatial memory systems theory posits that there are two types of memory system. One is a flexible, cognitive mapping system subserved by the hippocampal formation, and the other is a system centred on the striatum based on reinforcement learning principles where specific stimuli are associated with rewarded actions (O'Keefe & Nadel, 1978; White & McDonald, 2002). More recently, Khamassi & Humphries (2012) have argued that the division between model-based and model-free spatial learning is a better predictor of whether hippocampal or striatal systems will be recruited, with hippocampal systems associated with model-based responding and striatal systems with model-free responding. Model-free decision-making occurs when responding is based on average reward history associated with a particular cue-action pairing, whereas model-based decision-making allows knowledge of outcomes from previous learning history to be represented. We sought to test these theories by asking participants (N = 24) to navigate within a virtual environment through a previously learned, 9-junction route with distinctive landmarks at each junction, while undergoing functional magnetic resonance imaging. In critical conflict probe trials, a landmark was presented out of sequence such that following the usual sequence of actions would generate an opposite response to following the learned individual landmark-action association, now out of sequence. Participants that made sequence-based responses had higher parahippocampal activations relative to participants that made responses based on the individual landmark-action association, a result that would be predicted by the need to recruit model-based systems to make a sequence-based response. Parallel spatial memory systems theory would not predict hippocampal formation recruitment for either response in the conflict probe, because no cognitive mapping is required when following a prescribed route. In longer probe trials where participants were able to plan a sequence of responses, striatal systems were recruited (caudate and putamen) suggesting a role for striatum in action chunking.

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Declaration

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Chapter 1: Introduction

All mobile animals have evolved systems for maintaining their orientation with respect to known locations, as they navigate their environment in search of food, shelter, and conspecifics. Mammalian navigation uses inputs from vestibular, and other sensory systems, to maintain a sense of ongoing orientation with respect to a starting location, termed dead reckoning. Tasks such as efficient foraging or locomoting through featureless terrain rely on dead reckoning. For longer-term memory for significant locations and routes, representations involving landmarks and terrain features are required, as dead-reckoning is prone to accumulation of error, leading to disorientation (Dudchenko, 2010).

O'Keefe and Nadel (1978), building on the work of Tolman (1948), were the first to propose the existence of two fundamental types of spatial learning and memory, one for learning prescribed routes through the environment, and the other for flexible, map-like navigation, built up through combining dead-reckoning with landmark constellations during initial exploration of an environment. These two types of learning were thought to operate somewhat independently of each other, with the hippocampus being the critical structure supporting the mapping system. The discovery of hippocampal pyramidal cells responding when rats were in specific places in an environment, so called place cells, irrespective of heading direction and dependent on constellations of distal landmarks, further supported the existence of map-like hippocampal spatial representations (review in Hartley. Lever, Burgess & O'Keefe, 2014). Current formulations of parallel spatial memory systems theory will be reviewed, together with the behavioural and neurobiological evidence on which it is based (White & McDonald, 2002; White, Packard & McDonald, 2013). A key aspect of parallel spatial memory systems theory, is that both the type of learning

(latent or reward-based), and the type of information utilised (constellations of cues forming places or single cue-action associations), varies between systems. Prescribed route following within this framework engages the system based on single cue-action associations strengthened through reinforcement learning.

A reformulation of the theory based on different types of reward learning was proposed by Khamassi and Humphries (2012), as a better fit to the available data, de-emphasising cue type as a fundamental aspect of parallel systems. In their proposal, the division between model-based and model-free reinforcement learning (Sutton & Barto, 1998) is used to divide spatial tasks and the brain systems utilised for their successful solution, with model-free learning occurring when cue-action associations are strengthened by average reward history for that specific association, and model-based learning occurring when the organism is able to utilise information about the outcomes of chains of past actions to guide their current choices. Following a review of the Khamassi and Humphreys model, a critical perspective on remaining questions within both models will be summarised, prior to the rationale for the present research.

It will be argued that learning routes can involve not only learning about individual landmark-action associations, but also the sequence of landmarks occurring on the route, and the concatenated set of actions required in the series. Route sequence learning can be thought of as model-based learning, in that if a single cue along the route is altered, a prediction can still be made on appropriate action, such as a left or right turn, based on sequence knowledge. A novel route learning task in a virtual environment is utilised in the present research, learnt by adult participants while functional magnetic resonance imaging (fMRI) data is collected. By using probe trials to separate out, and sometimes conflict, individual landmark-action associations from route sequence knowledge, predictions arising from the differing

models of spatial memory systems can be tested, and a greater understanding of the brain systems underlying route learning can be gained. Traditional views would not distinguish the brain systems underlying individual association learning from sequence learning, as neither require flexible cognitive maps, whereas the theory of Khamassi and Humphries (2012) would distinguish individual landmark-action (model-free) learning from sequence (model-based) learning. Throughout the review, the lesional and neurophysiological non-human literature pertaining to spatial parallel memory systems theory will be drawn on necessarily selectively, although representative findings will be discussed, together with data that is hard to accommodate within current frameworks. The human fMRI literature directly addressing parallel spatial memory systems in navigation will be analysed in depth.

Parallel Spatial Memory Systems Theory: Original Formulation

In a comprehensive theoretical review paper, White and McDonald (2002) put forward a model of parallel memory systems involving the key structures of the hippocampus, dorsal striatum and amygdala, although the current focus will be on functioning attributed to the former two structures. They situated their model within a family of models making a distinction between procedural or habit-like memory systems and more cognitive, flexible systems (Sherry & Schacter, 1987). While the theory was not intended to apply only to spatial memory, the evidence base reviewed by White and McDonald pertains to spatial tasks, also the focus of the present research.

In parallel memory systems theory, the same information from the environment is processed in parallel, but in different ways, due to the different processing style of each system. The systems then interact, either competitively or cooperatively, to produce adaptive behaviour. The three systems analysed by White

and McDonald were labelled by the key brain structures thought to mediate learning in that system; the hippocampal, striatal and amygdala systems. The hippocampal system is thought to be responsible for rapid learning of relations between stimuli, such as constellations of cues about a common axis, forming a cognitive map. This system is driven by exploration of novelty, and learning occurs irrespective of reinforcement contingencies, although downstream structures can use hippocampal memory to inform response selection based on reward history (O'Keefe & Nadel, 1978). The striatal system underpins stimulus-response learning, where reinforcement gradually modulates the strength of association between a stimulus and an action. Stimuli can be individual cues, or in some circumstances scene "snapshots" treated as a single cue (O'Keefe & Nadel, 1978; White & McDonald, 2002). The amygdala system (not considered further here) is thought to underpin Pavlovian stimulus-reinforcer learning.

The neuroanatomy of the hippocampus is particularly suited to fast associative mnemonic functions as it receives input from all higher cortical association areas, with the recurrent axonal collaterals of the CA3 region of the hippocampus forming an autoassociative network, such that each CA3 cell has tens of thousands of synaptic connections with other CA3 cells (McClelland, McNaughton & O'Reilly, 1995; Rolls & Treves, 1998). This autoassociative neural architecture can bind together elements of experiences processed by diverse brain areas into a coherent pattern through Hebbian learning, which can then be retrieved by pattern completion processes when fragments of the original memory (cues) are experienced. i.e. the subset of CA3 cells activated by the cue, are then able to fire cells active during the whole original experience, as the connection between these cells will have strengthened during the original learning episode. In order to avoid interference from overlapping patterns, the

dentate input layer to the CA3 autoassociative layer carries out pattern separation functions through diverse mechanisms (review in Rolls, 2013), such that patterns with similar elements can be represented by different sets of neurons at the dentate level (Rolls & Treves, 1998).

In terms of dorsal striatal neuroanatomy, the circuitry involved is suited to the role of action selection modulated by reinforcement history (Shipp, 2017). This is because the striatum receives both "operative" input from cortex, where return connections from the basal ganglia to cortex via thalamus are thought to gate bids for action, as well as "contextual" input from cortex, without return connections, where sensorial and motivational context can influence action selection. Dopaminergic inputs from substantia nigra pars compacta and the ventral tegmental nuclei, serve to input reward information both for online action selection (a reward prediction signal) and as a modulator of learning between selected actions and reward outcomes (Pennartz, Ito, Verschure, Battaglia & Robbins, 2011; Shipp, 2017).

In the following sections, the lesional, pharmacological and human fMRI evidence underpinning the parallel memory systems proposal is considered. The focus in the non-human literature is on spatial tasks thought to reflect a reasonably "pure" dependence on hippocampal or striatal systems, where double-dissociation studies between hippocampus and striatum structures have been conducted. The human fMRI studies reviewed are modelled on these widely studied tasks utilised in rodent research.

Non-human studies.

The dual solution plus maze has historically been at the centre of debates concerning whether spatial learning occurs to places, or is based on responses to individual cues (O'Keefe & Nadel, 1978; Packard, 2009). In this task, rats are trained

to locomote from a starting location (for example, at the south end of one of the 4 arms of a cross-maze) and turn either right or left at the junction at the centre of the maze to locate a baited food well. Typically the straight ahead (north) arm has been blocked so that a T-junction is formed at the centre of the maze. A probe trial can be administered, after various amounts of training, in which the rat is positioned at the start of the opposite arm to that used in training. In intact animals soon after learning to criterion, a predominance of place responses are made during the probe trial, especially if the plus maze is set within a cue-rich wider environment. A place response is defined as a path taken to the same location as was rewarded during training, now requiring an opposite egocentric response (e.g. a left turn if training involved a right turn at the junction of the maze). After extended training however, rats predominantly repeat their egocentric response during the probe trial, thus going to the end of the opposite arm to that rewarded during training.

The mechanisms underlying this pattern of behaviour were clarified by Packard and McGaugh (1996). In their study, just after acquisition of the task after 8 days of training, one group of rats were administered a lidocaine anaesthetic injection causing reversible inactivation of the dorsal hippocampus, while another group was injected in the dorsolateral striatum. Two further control groups were administered saline at one or other of the injection sites. The probe trial starting from the opposite arm of the plus maze was then conducted. The group with hippocampal inactivation showed mixed responding, relative to the controls that showed a preponderance of place responding. Conversely, the group receiving dorsolateral striatum inactivation showed place responding. All groups were trained for a further 8 days from the habitual starting location, and again, prior to the probe trial were administered the same injections of lidocaine or saline. Now, saline groups showed a preponderance of

egocentric responses, as did the group with the hippocampal inactivation. The group with the dorsolateral striatum inactivation however maintained place responses.

Packard and McGaugh interpreted this pattern of results in terms of the hippocampal system forming a rapid representation of the place of the rewarded location, driving behaviour early on in training, as evidenced by the behaviour of intact animals, and animals with striatal inactivations, on the early probe trial. With further training a more habitual, egocentric response develops, driving behaviour in the late probe trial, in intact animals, and rats with hippocampal inactivations. The place response is not lost however, as the rats with dorsolateral striatal inactivations continue to show place responses even with overtraining. Within the parallel memory systems perspective both systems show learning, using a different set of the elements available in the task situation (place given by the cognitive map versus an egocentric response to the visual cue of the T-junction itself), with the hippocampal system showing more rapid learning early in training, and the striatal system showing slower learning. This slower learning is evidenced by a lack of clear egocentric responses in the rats with hippocampal inactivation early in training. In this study, competitive interactions between systems for control of behaviour in intact animals were inferred, with the hippocampal system "winning" early on, and the striatal response system gaining control after over-training.

Using lesion groups prior to acquisition of the dual solution cross maze task in rats, Oliveira, Bueno, Pomarico & Gugliano (1997) replicated the pattern of results obtained by Packard and McGaugh (1996) for the probe trial early in training; intact animals showed 60% place responses, rats with hippocampal lesions showed 0% place responses, and striatally-lesioned rats (mainly dorsolateral striatum) showed 50% place responses. This pattern of results only pertained in a cue-rich environment

however. In a cue-poor environment, although learning was not affected by lesion type, suggesting the integrity of the dorsolateral striatum is not necessary for egocentric response learning in the absence of cues, all groups showed a preponderance of egocentric responses in an early probe trial. It is possible these egocentric responses reflect a lack of distinction between training and probe trials with few orienting cues available. These researchers did not conduct a probe equivalent to the late probe trial of Packard and McGaugh (1996) in either type of environment.

Packard (1999) investigated the effects of administering glutamate as a memory-enhancer to both the hippocampus and dorsolateral striatum after early acquisition on the dual response task. If glutamate acted to consolidate memory for either a place or egocentric response, these effects should be evident in probe performance. In control rats, the pattern of a preponderance of place responses on the early probe trial, and egocentric responses on the late probe trial was replicated (Packard & McGaugh, 1996). In rats with glutamate injections to the hippocampus, place responses were observed both early and late in training, so the apparent cementing of hippocampal memory early in training seemed to prevent an egocentric habit from dominating behaviour late in training. In rats with glutamate injections to the dorsolateral striatum, a robust egocentric response was seen during the early probe, maintained in the late probe, suggesting the memory enhancement effect both accelerated learning in the dorsolateral striatum, and caused the egocentric response to dominate over the hippocampal place response earlier than in control animals.

A second well-studied paradigm within the parallel spatial memory literature is a variant on the widely used Morris water maze task (Morris, 1981). In the original task, rats learn the location of a submerged escape platform in a large circular tank of

opaque water, using distal room cues to code the platform location (Fenton, Arolfo, Nerad, & Bures, 1994), eventually taking direct swim paths from any starting point to the location of the escape platform on probe trials. Rats with hippocampal lesions are strongly impaired on this task (Morris, Morris, Garrud, Rawlins, & O'Keefe, 1982). McDonald and White (1994) carried out a variation of the water maze developed by Sutherland and Rudy (1988) in which the escape platform is visible throughout training, followed by probe trials where the platform is in the same location, but is just under the surface and therefore not visible. Finally, the visible platform is moved from its previous location to a different quadrant in the pool. The study consisted of a fimbra-fornix lesion group (impairing hippocampal function), a group with dorsolateral striatal lesions, and an unoperated control group. All groups were equally fast at acquiring the cued platform escape behaviour, as measured by speed and directness of swim paths to the platform. Consonant with previous literature, the group with fimbra-fornix lesions were impaired on hidden platform probe trials, showing a lack of place coding, whereas the other two groups were unimpaired. Interestingly, in the final visible platform probes with the platform in a new location, a double dissociation occurred, whereby 7 out of 9 rats with dorsolateral striatal lesions first swam to the old place where the platform had been, before then swimming towards the visible platform. All of the 8 hippocampally-impaired rats swam directly to the new, visible platform location. The control rats were split equally in terms of first making a place response or a visible platform response. McDonald and White suggested that the behaviour of the control rats showed the competitive interaction between functioning place (hippocampal) and stimulus-response (dorsolateral striatum) systems, each driving a different behavioural response, to the old place versus new visible location respectively. The lesion groups showed the

behavioural output of each system exclusively in the first response, either showing place or stimulus-response behaviours, depending on which system was functionally intact.

Further evidence for the dissociability of hippocampal and dorsolateral striatal systems for supporting place and cued versions of Morris water maze performance came from findings that a post-training memory enhancer (amphetamine) administered to both brain areas only enhanced place performance in the hippocampal group, and only enhanced cued platform escape latencies in the dorsolateral striatal group (Packard, Cahill & McGaugh, 1994). Conversely, post-training injections of a memory blocker (an *N*-methyl-D-aspartate antagonist) in both hippocampus and dorsolateral striatum only impaired retention of the place task in the hippocampal group, and only impaired escape latency to the visible platform task in the dorsolateral striatal group (Packard & Teather, 1997). In both these studies, the place task consisted of the usual Morris water maze hidden platform task, followed by a test trial 24hrs post-training. The cued platform task consisted of training where the platform was visible and changed locations on each trial, followed by a test trial to a new visible location after 24hrs post-training.

A final paradigm widely used in the rodent literature on parallel spatial memory systems consists of variations on the 8-arm radial maze task (Olton & Samuelson, 1976). McDonald and White (1993) used two tasks on the 8-arm maze. The first, win-shift task, required rats to enter one of the arms of the maze from the central location, to retrieve a food reward in a well at the end of the arm. On returning to the central location after food consumption, after 10s the rat could again select an arm to enter to gain food reward. The maze was set within a cue-rich wider laboratory. All 8 locations in the maze are baited initially, so the most efficient

strategy is to only enter each arm once. Performance is measured by the mean number of errors (revisits of previously baited arms) made in the first 8 trials, across testing sessions. Three groups of rats were tested on this task; controls, rats with fimbra-fornix lesions, and rats with rather extensive lesions of the dorsal striatum, encompassing both dorsolateral and all but the most medial parts of the dorsomedial striatum. As predicted, rats with fimbra-fornix lesions made 3-4 times more errors than the other two groups, that did not differ from each other. These results were interpreted as demonstrating that the hippocampal system was necessary for remembering the places of previously visited locations.

A second, "win-stay" task (McDonald and White, 1993) involved trials in which a pseudorandom set of 4 arms were lit (no more than 2 adjacent to each other), and only the lit arms were baited. Once the reward was consumed, the lit arm was rebaited for a second time. After consumption, the light was switched off and no further reward was provided. Performance was measured by the percentage of correct choices (maximum 8) out of all arms visited (or lit arm visits divided by the total number of arms visited). The availability of extramaze laboratory cues was diminished by dim lighting. The performance of control rats plateaued at approximately 80% correct choices, whereas that of rats with dorsal striatum lesions was approximately 50% correct. Rats with fimbra-fornix lesions reached peak performance faster than controls. McDonald and White interpreted these results as suggesting that the dorsal striatum was necessary for forming the stimulus-response associations between lit arms and approach behaviour. Conversely, an intact hippocampus may impair task acquisition, because place representations of rewarded locations are remembered, leading to avoidance of these locations i.e. a natural tendency to treat the task as a spatial win-shift task.

In summary, the three spatial paradigms reviewed above have provided the clearest evidence of lesional double-dissociations between striatal and hippocampal systems, whereby stimulus-stimulus relations in the form of place representations reflect the processing style of the hippocampal system, and instrumental stimulus-response associations reflect the processing style of the striatal system (White & McDonald, 2002). In the following section, fMRI studies directly inspired by the double-dissociation paradigms and theory outlined above will be reviewed. The review of further fMRI studies will be postponed to following sections, after re-formulations of parallel spatial memory systems theory emphasising heterogeneity of function within the dorsal striatum, arising from lesional and neurophysiological studies, are considered. Anticipating discussion of the fMRI studies, two major issues arise. The first is that a central postulate of parallel memory systems theory is that information flows through each system and is processed continuously, with a greater or lesser coherence of learning occurring, depending on the task situation compatibility with the processing style of each system. Therefore, it is unclear whether differences in levels of activation as measured by fMRI blood oxygen level dependent (BOLD) responses would provide a useful measure of level of engagement of one system versus another in producing behaviour. A second issue is that while the studies below were inspired by the tasks and findings reviewed in this section, the tasks used in the fMRI studies depart considerably from these paradigms, thus making direct links to the lesional literature more problematic.

Human fMRI studies.

In an influential first study addressing parallel spatial memory systems, Hartley, Maguire, Spiers & Burgess (2003) used two virtual environments (VEs) modelled on city centres to create 3 tasks, a wayfinding task, a route-following task,

and a control, trail-following condition. In the wayfinding task, during pre-training participants were allowed 15 mins of free exploration of the VE. During scanning, participants were exposed to the VE for 50 s (repeated 8 times in total across 8 experimental blocks), during which time they would be placed at a starting point, with a picture of a target landmark building available in the corner of the screen. Their task was to navigate the shortest route from their starting point to the target landmark. No two routes were repeated across the experiment. This task requires a flexible, map-like representation, and thus would be expected to require the hippocampal system during performance.

In the second VE, participants learnt a fixed, 9-landmark route through the VE, and their task was to go to the next landmark along the route, also shown on the corner of the screen. This condition also lasted for 50s and was repeated across 8 runs. Pre-scanning learning involved following a trail of green blobs along the route, where they became gradually more interspersed until they were unnecessary for successful performance of the route. With reference to the work of Packard and McGaugh (1996) and O'Keefe and Nadel (1978), the authors argued that this route-finding task would draw on stimulus-response striatal mechanisms, particularly with the over-learning of the route. Finally, a 50s condition involving following a trail of blobs between landmarks in the VE used for the wayfinding task was used as a trail-following control condition. Thus similar distances were traversed in the same environment in this control condition relative to wayfinding, but no spatial memory or computations were required. This condition was also repeated across 8 runs.

Participants reached ceiling performance in the route-following task, but not in the harder wayfinding task. In the contrast between the wayfinding task and the trail-following control, a large set of brain areas often activated in navigation-related tasks

were observed, including areas of prefrontal cortex, parietal cortex, retrosplenial and parahippocampal cortices, although unexpectedly, not the hippocampus itself. Higher activation of the body of the caudate nucleus of the striatum was observed. In the contrast between route-following and trail-following, higher activation in the body of the caudate nucleus was also observed, as well as areas of prefrontal cortex. Despite the lack of greater hippocampal activation in wayfinding relative to trail-following within the same VE, there was a within-subjects correlation between less error, measured by the discrepancy between path taken and the ideal path on each trial, and higher right posterior hippocampal activation, with the right insula also showing this correlation (a 10-voxel extent at $p < 0.01$ was used as a threshold).

Between-subjects correlations were performed, with each participant being assigned a summary measure of their wayfinding performance, based on their overall mean deviation from ideal paths in the wayfinding condition. This performance measure was correlated with activations for voxel clusters active in the wayfinding-route-following contrast, and the route-following – wayfinding contrast. Several cortical areas showed above threshold correlations with the wayfinding – route-following contrast, whereas only the right caudate head showed an above threshold negative correlation between performance and the route-following – wayfinding contrast.

In interpreting the pattern of results obtained, the authors argued that because stimulus-response, or "action-based" representations, as well as cognitive map representations, are available in parallel, good performance involves selecting the right representations for the task at hand. In the case of the wayfinding condition, involving many novel routes, selection of the striatal, stimulus response, system would lead to poor performance, as following previously experienced successful

routes is unhelpful. Thus poor navigators show higher right caudate activations in the wayfinding condition versus route-following, because they are applying the wrong system to the task, whereas good navigators are showing higher caudate activation in route-following relative to wayfinding, because they are applying the right system to the task, relative to wayfinding. No such between-subjects correlations with hippocampal activations occurred for the wayfinding – route-following contrast, because selection of the hippocampal system in the route-following task does not adversely affect performance. This line of argument pre-supposes that the process of selecting which system guides behaviour during task performance leads to greater activations for that system. The biological mechanism that would underpin such a link between selection and activation is unclear. The authors also argue that the higher activation found in the caudate body in both wayfinding and route-following relative to trail-following suggests a more general role for this region, relative to the task-specific performance-related involvement of the caudate head, although this more general role is not specified further.

Another early study was that of Iaria and colleagues (Iaria, Petrides, Dagher, Pike & Bohbot, 2003). There researchers used an 8-arm radial maze within a VE, whereby the starting point was the same each time, although participants were not alerted to this fact. In experimental conditions, participants had to collect 4 objects hidden at the end of 4 baited arms, and after an interval, avoid these arms and retrieve objects from the previously unvisited arms. Distal landmarks were available which could be used to code the place of objects during the initial retrieval phase. In probe trials, distal landmarks were obscured when participants had to visit the unbaited arms, having experienced the initial retrieval phase with the distal landmarks present. Participants were divided into those that always used a verbal counting strategy to

visit the correct arms of the maze, having realised the starting point was always similar, and those that initially used a spatial coding strategy using the distal landmarks, and then shifted to a counting strategy in later runs, having realised that this was a more fruitful strategy during the unexpected probe trials. In early scans, those that used a spatial strategy showed higher right hippocampal activation relative to a control condition collecting visible objects, whereas those using a non-spatial counting strategy showed greater caudate and putamen activation relative to the control condition. The authors argued that these results were consistent with the parallel spatial memory systems perspective of White and McDonald (2002), despite the lack of clear correspondence between using a memorised verbal list of arms to visit in the human radial maze paradigm, and utilising learned cue-action associations in the non-human radial maze research.

A novel approach attempting to link the lesional literature with brain systems in human navigation was taken by Marchette, Bakker & Shelton (2011). They developed a VE navigation task conceptually inspired by the rodent dual solution crossmaze task (Packard & McGaugh, 1996). In this task, participants passively learned a fixed route through a VE consisting of an irregular grid-like pattern of linked routes. Along the route, 12 objects were placed, and participants were asked to remember the objects and their locations for future retrieval. During retrieval, three different types of trial were provided. In the first, the shortest route from the starting location of the participant and the target object they were required to retrieve involved a stretch of the familiar route. In other trials, a short-cut through the VE was possible, of similar length to using a segment of the learned route. In a final third of trials, a shortcut route was both possible, and shorter than use of the learned route. Interestingly, participants were not primed that they could take shortcuts during

retrieval; several participants noticed the untraversed alleyways during encoding of the prescribed route, and inferred the linkages between alleyways.

There were large individual differences between participants in whether they took shortcuts, or used segments of the learned route to retrieve objects from diverse starting positions, and these differences correlated with performance on a test of spatial perspective taking (Kozhevnikov & Hegarty, 2001). Marchette et al. (2011) were interested in whether differences between brain activation during encoding of the route would correlate with retrieval performance across participants. The learning of the route was conducted during fMRI scanning. In total there were 12 passive displays of movement through the route in the VE, interspersed with a control condition involving observing red or blue balls appearing in randomly arranged passageways of a grid-like VE. Immediately after scanning, the retrieval task was conducted, from which the index of short-cutting trials was derived for each participant. Activations surviving a whole brain contrast between learning and control conditions were used to define clusters of activation within 4 regions of interest; the right and left hippocampus and the right and left caudate nucleus. A positive but non-significant correlation occurred between the mean activation (across the voxel cluster) in the hippocampus and amount of shortcutting behaviour, and a negative, but again non-significant, correlation occurred between shortcutting behaviour and magnitude of mean caudate activation. The authors derived an index of the normalised ratio of hippocampal to caudate activation, and this measure did correlate reliably with degree of shortcutting behaviour.

In a follow-up study in which scanning occurred both for encoding and object retrieval performance, the correlation between relative hippocampal to caudate activation, and shortcutting performance was replicated, both for the learning phase of

the study, and during task performance (Furman, Clements-Stephens, Marchette & Shelton, 2014). Interestingly however, there were no differences observed between contrasts of trials in which short-cutting occurred, versus trials in which segments of the familiar route occurred, either at whole brain level, or within the 4 regions of interest. This finding contrasts somewhat with the within-subjects correlation observed in Hartley et al. (2003) between short-cutting performance and right hippocampal activation. The authors argue that the hippocampal to caudate activation ratio reflects a stable bias to access hippocampal versus striatal systems, rather than being a reflection of which system is driving performance at any one time. Again, this view contrasts with the argument made in Hartley et al. (2003), that access to one system or the other to drive performance is related to differences in activation in hippocampal and striatal regions between good and poor navigators.

It is worth noting that although both the Hartley et al. (2003) and Marchette et al. (2011; Furman et al., 2014) studies were motivated by the dual solution plus maze study of Packard and McGaugh (1996), unlike this study, a complex multi-junction route is utilised. In terms of lesional studies within the rodent literature, performance in complex mazes in which distinctive cues do not mark junctions, are impaired by both hippocampal lesions (Bresnahan, Kametami, Spangler, Chachich, Wiser & Ingram, 1988; Kametani, Bresnahan, Chachich, Spangler & Ingram, 1989; review in O'Keefe & Nadel, 1978) and striatal lesions (Pistell, Nelson, Miller, Spangler, Ingram & Devan, 2009), with striatal lesions showing the greatest level of impairment.

In terms of trying to account for hippocampal lesion impairment in complex route following, O'Keefe and Nadel (1978) focused their discussion on indications in the literature that intact rats are more likely to enter blind alleys that occur in the correct direction to the goal. Thus knowing the relative place of the goal can be

helpful in complex maze learning for the elements that are in the goal direction, by definition a majority of the elements, a function possibly disabled with damage to the hipocampus. However, O'Keefe and Nadel acknowledged that this direction factor could not fully account for either the lesional impairments, or some of the behavioural patterns seen during learning in intact rats, a point which will be returned to in later sections on types of learning algorithms that may be required in different types of task.

When considering the severe impairment in complex route-following with striatal lesions, Pistell et al. (2009) refer to the association of striatal function with procedural memory, predicting that striatal lesions will impair performance on a complex maze without distinctive cues because a sequence of egocentric stimulus-response elements are involved. The validity of conceptualising a sequence of responses on a complex maze in this way will be returned to in the final section of this review, providing the rationale for the present research. A pertinent difference between the rodent studies and the complex routes used in the human fMRI studies of Hartley et al. (2003) and Marchette et al. (2011; Furman et al., 2014) is that in these VE routes, distinctive landmark cues are provided that distinguish most of the critical junctions. It is not known as yet what the effects of either hippocampal or striatal lesions in rodents would be on complex route-following mazes with these characteristics, as the relevant studies have not yet been performed, to the author's knowledge. When choices as to the correct left or right turn are signalled by a single cue, such as a white versus black door, or a differently textured floor covering, rats with hippocampal lesions are unimpaired (Leaton, 1969; Wincour & Breckenridge, 1973), but effectively such a manipulation simplifies the task to a single stimulus-

response association, and therefore is not analogous to the VE routes utilized by Hartley et al. and Marchette et al.

An influential study taking a different approach to translating the tasks used in the non-human lesional literature to fMRI studies, was conducted by Döeller, King and Burgess (2008). This study was directly inspired by water maze studies distinguishing place versus cue-guided goal localisation, although with an important difference relative to the visible platform studies of McDonald and White (1993). The authors followed the paradigm developed by Pearce, Roberts and Good (1998), in which rats with hippocampal lesions had to locate an escape platform in a Morris water maze, where both external room cues were available, and a landmark at a constant distance (25cm) and direction from the platform, was available. Within a daily testing session, the platform remained in the same location, so could be found either by use of external cues, or through use of the landmark together with direction information, provided by room cues. Between testing sessions, the platform and landmark changed positions within the pool, so external cues could not be used to locate the platform, only directional use of the landmark remained reliable. Rats with hippocampal lesions were faster at locating the hidden platform at the start of a testing session relative to controls, because control rats had a tendency to swim to the previous place where the platform had been with respect to the external cues. However, by the end of the testing session, controls were outperforming rats with hippocampal lesions, whose performance did not vary reliably within sessions. Swim paths were reasonably direct in hippocampal rats, so they were learning how to use the landmark to locate the platform, as opposed to showing consistently poor performance.

The difference between the Pearce et al. paradigm and the visible platform studies of McDonald and White (1993) was that use of the landmark requires directional information; it is insufficient to swim towards the landmark cue itself. While the Pearce et al. (1998) results suggest that hippocampal rats can achieve this vector navigation, it is unclear which brain system is underpinning this ability, a point which will be considered further below. Döeller et al. considered that striatal mechanisms were most likely, and thus a VE task analogous to the Pearce et al. paradigm could help uncover parallel spatial memory systems in human navigation.

In the study of Döeller et al. (2008), participants were placed in a large, cliff-like circular enclosure, with distal landmarks set at infinity acting as distal directional orienting cues. Within the enclosure, there was a single radially symmetric landmark (a traffic cone). During a learning phase, a set of objects were positioned within the enclosure, and participants were required to retrieve them and remember their locations. In a test phase, a picture of one of the objects was provided, and the participant had to navigate to the location which they thought had contained the object. Once the participant has indicated the location, they would receive feedback in the form of the object appearing at its original location, before the start of the next trial. The critical manipulation involved moving the landmark between blocks of trials, with half of the target objects shifting with the landmark (maintaining the same distance and direction relative to the landmark), and the other half of the target objects remaining in place, with respect to the circular boundary and orienting cues.

Döeller et al. (2008) focussed their analysis on performance-related effects, rather than reporting direct contrasts between landmark- or boundary-related objects. They modelled the cue, replace and feedback phases of the task as separate conditions, and included a parametric modulator for the replace phase, which

reflected the extent to which participants selected a boundary-related location, or a landmark-related location. The experiment consisted of 4 blocks of trials, so a boundary-related location for an object that followed the landmark could be based on the first block of trials, or a subsequent block. The location with the least error was selected in these cases. During the feedback phase, a parametric modulator was introduced reflecting the degree of error on the subsequent trial with that object, the rationale being that the lower the error on the subsequent trial, the greater the learning that had occurred as a result of feedback.

For the replace phase, the right caudate head showed significant activation, modulated by landmark influence, although there was no corresponding result for the hippocampus reflecting boundary influence. For the feedback phase, the right caudate head showed significant activation, following modulation by degree of landmark-related learning, and the right hippocampus showed activation modulated by degree of boundary-related learning. These results were interpreted in terms of parallel systems, with striatal systems underpinning learning to the landmark, and hippocampal systems underpinning learning of place with respect to the boundary, with distal cues providing directional information to both systems. There was also a generalised spatial novelty effect in right anterior hippocampus, as measured by modulation of response across trials within blocks, with decay of activation occurring between trials 1-2 versus 3-4.

Döeller et al. further investigated how the caudate and hippocampus interact to potentially produce behaviour during the replace phase, by using dynamic causal modelling. They found that right medial prefrontal cortex activity was correlated with joint activation or deactivation of the right caudate and right hippocampus, a finding interpreted as suggesting that when both systems are equally active, the medial

prefrontal cortex may arbitrate between different behavioural responses driven by the different systems. This correlation was not found for feedback phase activations in hippocampus and caudate, with the authors suggesting that this phase corresponds to learning rather than online action selection.

Following the study of Döeller et al., Kosaki and colleagues (Kosaki, Poulter, Austen & McGregor, 2016) addressed the question of the brain system underlying coding of location with respect to a landmark-goal vector, by conducting a lesional study with rats. In their first study, three groups of rats, one with dorsolateral striatal lesions, one with hippocampal lesions and controls, were tested on the Pearce et al. (1998) moving landmark task. In a probe trial with the landmark in a novel position at the centre of the pool relative to training locations, hippocampal and control groups searched the correct location, now without the escape platform, more than an opposite equivalent location. Rats with dorsolateral striatal lesions did not distinguish the two locations, although they did show a faster latency to reach both the correct and opposite goal location. In a follow-up experiment, the external environment was further cue-enriched, and under these circumstances the impairment in the dorsolateral lesion group was not found. These results support the proposition that the hippocampal rats may have been using striatal systems to solve the moving landmark vector task of Pearce et al., as suggested by Doeller et al. (2008). Conversely, Guderian and colleagues (Guderian, Dzieciol, Gadian, Jentschke, Doeller, Burgess, et al., 2015) found that patients with hippocampal atrophy were equally impaired in learning goals relative to landmarks or the boundary in the Doeller et al. (2008) task, a result not predicted if striatal systems underpin learning to the landmark. However, poor performance could have arisen due to a number of factors, so it is difficult to draw firm conclusions from these negative findings.

A final study considered in this section is that of Wegman and colleagues (Wegman, Tyborowska, & Janzen 2014), aimed at testing the distinction between navigating using a configuration of landmarks, traditionally thought of as a hippocampal function, and navigation based on a vector from a single landmark, hypothesized to be a striatal function, following Doeller et al. (2008). Participants viewed an array of 3 distinctive landmarks in a VE without boundaries, together with a target location marked by a tall structure. Directional information was provided by shadows on each of the landmarks, rather than distal cues. The actual configuration viewed varied from trial to trial, and following an encoding phase, participants could navigate to the remembered location of the goal from different starting points in the VE. The retrieval phase consisted of two types of trials, one where only one landmark from the array was present, together with the directional shadow, and the other where two of the 3 landmarks of the array were present, with no shadows. Single shadowed-landmark retrieval trials and shadowless configuration trials were blocked, and additionally participants were primed during encoding as to which landmark would be present during single landmark trials, and were primed with a single landmark (from the two present) during shadowless configuration trials, to try to equate cueing events between the two trial types. The cueing procedure allowed participants to engage in a memory strategy during encoding, and this difference was reflected in contrasts between the trial types, with greater hippocampal activation when retrieval involved the configuration of landmarks, and greater caudate activation when retrieval involved a single, shadowed landmark.

The results of Wegman et al. (2014) are consistent with traditional parallel memory systems theory, although less consistent with the emphasis on the necessity of boundaries for hippocampal place coding (Doeller et al., 2008). It is interesting to

note that unlike previous studies, differences between hippocampal and caudate activations emerged from contrasts between trial types, whereas such direct differences have been elusive in the other studies reviewed in this section. Instead, different types of performance-related variables have correlated with either hippocampal or caudate activation.

In summary, several studies have adapted tasks used in the non-human literature on parallel spatial memory systems to investigate the functioning of the systems in human navigation. While there is some consistency in key brain structures that are implicated in map-like and single-cue guided learning, e.g. hippocampus and caudate nucleus of the striatum, the actual measures vary considerably between studies, with some only finding associations based on between-subjects individual differences (Hartley et al., 2003; Iaria et al., 2003; Marchette et al., 2011), others finding within-subjects performance-related associations (Doeller et al., 2008; Hartley et al., 2003) and finally only one study finding a difference in activations levels between different trial types accessing mapping or landmark-vector navigation (Wegman et al., 2014).

In the following section, consideration will be given to important developments in the non-human literature on parallel spatial memory systems, in which heterogeneity of function within the striatum is hypothesized. Specifically, the dorsolateral striatum in rodents (analogue to putamen in humans) is associated with S-R learning and habit formation, and the dorsomedial striatum (caudate in humans) is considered to be form part of a "cognitive" processing loop, including the hippocampus (Yin & Knowlton, 2006), leading to a revised formulation of parallel spatial memory systems theory (Devan, Hong & McDonald, 2011; White, 2009; Yin & Knowlton, 2006). Both non-human lesional and neurophysiological studies, and

human fMRI studies providing evidence for this heterogeneity of function will be reviewed, and the question of how to interpret associations with caudate (as opposed to putamen) activation in human fMRI studies such as those reviewed above, will then be discussed.

Parallel Spatial Memory Systems Theory: Current Formulations

Although not the focus of the theoretical review paper of White and McDonald (2002), stating their parallel spatial memory systems theory, there were already indications of diversity of function within the dorsal striatum. Influenced by anatomical investigations in the rat, chiefly the work of McGeorge and Faull (1989) showing a predominance of motor and sensorimotor projections to the dorsolateral striatum, and sensory and associative projections to dorsomedial striatum (including hippocampus and other media temporal lobe structures), Devan and White (1999) investigated whether dorsolateral and dorsomedial lesions produced differential effects. Utilising the cued version of the Morris water maze, they investigated learning of the cued platform location, performance on probes in which the platform was hidden, and performance on a probe in which the location of the visible platform was moved. Four groups of rats were tested; sham controls, a fimbra-fornix lesion group, a dorsolateral striatum lesion group, and a dorsomedial striatum lesion group. All groups were able to learn to swim to the visible platform, and only the fimbra-fornix lesion group showed a persisting deficit in finding the platform when it was hidden, although the dorsomedial striatum lesion group showed an early deficit. On the final probe trial with the visible platform moved to a new location however, both the fimbra-fornix group and the dorsomedial lesion group swam first to the new cued location, in contrast to the dorsolateral lesion group, that swam to the previous place. The sham group were approximately equally split between first swimming to place or

new cued location. These results suggested that both hippocampus and dorsomedial striatum were involved in place responses, although in different ways; the hippocampus was necessary for place coding, whereas the dorsomedial striatum appeared to be involved in expressing a place response, without being fully necessary for this expression however (Devan & White, 1999).

Further evidence for differentiation of function between dorsomedial and dorsolateral striatum was provided by Yin and Knowlton (2004), using the dual solution crossmaze. Relative to rats with dorsolateral striatum lesions as well as shams, those with posterior dorsomedial lesions made very few place responses both on early and late probe trials, where the starting arm of the T-junction was reversed, suggesting a role for posterior dorsomedial striatum in place responding. The theoretical position developed by Yin and Knowlton (2004; 2006) from results such as these within the spatial literature, as well as non-spatial conditional instrumental learning tasks (review in Yin and Knowlton, 2006) and anatomical considerations (Alexander, Crutcher & DeLong, 1990), was that the appropriate unit of study should be the cortico-basal-ganglia loop, rather than treating basal ganglia nuclei in isolation. Within this framework, the dorsolateral striatum can be considered part of a sensorimotor loop, involved in habit-formation, whereas the dorsomedial striatum can be considered part of a "cognitive" or associative loop, comprising large parts of neocortex, and including parts of allocortex such as the hippocampus. Within this scheme, the dorsomedial striatum (caudate in primates) collaborates with hippocampus and associative cortex by utilising flexible representations of goal states, carrying out the function of appropriate action selection based on these representations. In contrast, the dorsolateral striatum (putamen in primates) is involved in stimulus-response habit formation. Reviews by Devan et al. (2011) and

White (2009) support this division of function between dorsolateral striatum being involved with S-R reinforcement learning and habit formation, and the dorsomedial striatum being concerned with more rapid and flexible response-outcome learning. Within the theoretical perspective of Yin and Knowlton (2006), less emphasis is placed on the independence of learning within the parallel systems, and more emphasis is placed on cross-talk between the circuits, as a way of explaining the gradual ascendance of habitual control over behaviour with experience.

In the following section, the neurophysiological evidence, gained from single-cell recording in rat striatum during spatial tasks, is reviewed as it relates to diversity of function within the striatum. Studies using fMRI directly testing predictions from this reformulation of parallel spatial memory systems theory will be reviewed after the following section. The implications of the current formulation of parallel memory systems, emphasising diversity of function between dorsolateral (putamen) and dorsomedial (caudate) striatum, on interpretation of fMRI findings reviewed in section the previous section where caudate activation has been associated to stimulus-response behaviour, will also be considered.

Non-human neurophysiological studies.

Early studies sought to establish whether striatal neurons displayed spatial firing properties such as those found in the hippocampus (place cells; O'Keefe & Dostrovsky, 1971) or dorsal thalamus (so called head head-direction cells which become active for a particular direction of facing in an environment, irrespective of place; Taube, Muller, & Rank, 1990). Mizumori and colleagues (Mizumori, Ragozzino & Cooper, 2000; Ragozzino, Leutgeb & Mizumori, 2001) in a series of studies utilizing an 8-arm radial maze win-shift task with rats, measured task-related responses from dorsomedial striatum. Approximately 40% of cells showed task

related responses, about 10-15% of which displayed head-direction cell properties, i.e. activity based on a particular heading direction irrespective of location on the maze. These head-direction cells were only found in the ventro-caudal part of the dorsomedial striatum (see also Wiener, 1993), where retrosplenial and entorhinal cortex inputs were reported by McGeorge and Faull (1989). Task-related responses were a mixture of location modulated by direction on the maze, generally with activity on more than one arm of the maze, unlike hippocampal place cells. A minority of cells showed turn-related or reward-related responses.

With a more explicit focus on measuring dorsal striatal neuronal activity in sequences of spatially-guided behaviour, Schmitzer-Torbert and Redish (2004; 2008) measured dorsal striatal neuronal responses during a multiple T task. In this task, rats learn a set of 4 junctions in a multiple T-maze, ending in appetitive reward either to the left or right of the final junction. Over different testing sessions, different combinations of left and right turn junctions (i.e. different routes) are learnt, allowing neuronal responses to be examined in terms of different types of turning responses in the same place, or within a different set of sequences. The authors found that out of the approximately 40-50% of task-responsive cells, a small majority were responsive to actions taken in particular locations during specific sequences, and the rest were responsive to reward delivery, usually at just one out of the two possible food locations. Although both cells in dorsolateral and dorsomedial striatum were sampled, they were not reported as separate subsets of recordings. Turn-dependent location responsiveness was not found in a task where distance travelled from last food reward, situated in a different start location each time, was rewarded, as opposed to a destination at the end of a spatially consistent trajectory as in the multiple T maze (Schmitzer-Torbet & Redish, 2008). The authors interpreted these findings as

demonstrating that striatal cells code a combination of spatial cue and action within a sequence, only if such spatial information is reliably linked to rewards (see also Berke, Breck and Eichenbaum, 2009, for equivalent findings). Such an interpretation for the maze-responsive neurons would be consistent with a stimulus-response function, as well as an action-chaining function. The reward-related neuronal population would be consistent with some form of action-outcome coding, hypothesised to occur in dorsomedial striatum (Yin & Knowlton, 2006).

Comprehensive study of neuronal responses in dorsomedial and dorsolateral rat striatum has been undertaken by Graybiel and colleagues (Barnes, Kubota, Hu, Jin & Graybiel, 2005; Thorn, Atallah, Howe, & Graybiel, 2010; Thorn & Graybiel, 2014), with the aim of examining differences between these areas, as tasks are learned and overlearned (i.e. become habitual and resistant to reward-devaluation). A conditional T-maze task was utilized, such that after a warning click, signaling the start of a trial and the lifting of a start gate, the rat could run along the stem of the T. Two different tones could then be activated (in random presentation), each associated with a different location (right or left at the T-junction) for reward at a food well at the end of the T arms. Such a task makes very explicit cue onset, thus permitting assessment of cue-responsive cells that would be expected in a brain area underpinning the learning of stimulus-response pairings. Rats were trained until they reached asymptotic performance (over 70% correct), and training continued to a habitual phase, where performance of the task continues despite reward devaluation or absence.

There were clear differences in patterns of ensemble responses across dorsolateral and dorsomedial striatal regions, particularly as task learning progressed. An early, “task-bracketing” pattern was observed in dorsolateral striatum, whereby

task-responsive medium spiny projection neurons were most active and consistent at the start and end of the task, i.e. warning click and goal reaching. This pattern continued throughout all phases of training, being strong in the "overlearned" phase of the task. In dorsomedial striatum, at task acquisition, most neurons were responsive during the middle of the task, prior to and after the conditional cue and turn selection. This pattern waned during the overtraining phase however, as indicated by a decline in entropy of ensemble firing, a measure of consistency of firing across task events.

Thorn et al. (2010) interpreted these results in terms of a task set being established early in dorsolateral striatum, not only before the habitual phase of task mastery, but before performance asymptote was reached. This task set is not fully expressed until dorsomedial activity wanes however. These results are consistent with the idea that dorsolateral striatum subserves habitual behaviour, and dorsomedial striatum is involved in outcome-related flexible choice behaviour. A surprising aspect of their results however was the lack of cells in either area directly responsive to the cue, with most turn-related responses occurring during and after turns had been executed. It may be expected that in an area such as the dorsolateral striatum associated with stimulus-response learning, there would be clear cue-related responses. A further unexpected finding, although consistent with the results of Schmitzer-Torbet and Redish (2004; 2008), was the reward-related cells found in both dorsolateral and dorsomedial striatum. These results are not consistent with a strict stimulus-response function in dorsolateral striatum, whereby reward is only represented by the change over time in the strength of stimulus-response bonds, rather than outcomes being explicitly represented.

In a theoretical review paper, Smith and Graybiel (2016) argue that the body of neurophysiological work on the rodent striatum suggests that the role of

dorsolateral striatum in habitual behaviour may be more linked with the chaining and fine-tuning of motor sequences. However, they acknowledge that an absence of overtly cue-responsive neurons cannot be taken as sole evidence for a lack of stimulus-response coding; indeed other classes of neurons within the striatum may carry relevant stimulus information. Kubota and colleagues (Kubota et al., 2009) found that GABAergic interneurons in dorsolateral striatum were responsive to changes in rewarded action-signalling cues (see also Berke et al., 2009). Smith and Graybiel also argue that even dorsolateral striatum may have some role in outcome signaling, given similar numbers of reward responsive neurons in dorsolateral and dorsomedial striatum. The debate concerning how reward and action outcomes may be represented in diverse brain systems is discussed further below, when models which emphasize formalisms of different types of learning mechanism across sensorimotor and associative cortico-basal ganglia loops are considered. In the following section, fMRI studies using spatial tasks, explicitly aimed at testing the reformulation of parallel memory systems theory emphasizing diversity of function within the striatum (i.e. putamen as part of sensorimotor loop, and caudate as part of associative loop), will be reviewed.

Human fMRI studies.

In a series of studies, Brown and colleagues (Brown, Ross, Keller, Hasselmo & Stern, 2010; Brown, Ross, Tobyne, & Stern, 2012; Brown & Stern, 2014) have examined the hypothesis that hippocampus and caudate nucleus collaborate in situations where similar constellations of stimuli lead to different behavioural choices depending on contextual information (Devan et al., 2011; Yin & Knowlton, 2006). In their design, participants learnt to navigate a set of 4-junction routes through different "museum" corridors, with each corridor containing distinctive wall textures and

exhibits. Participants experienced passive, 2.5 s navigation along a corridor, and then were required to respond by signalling whether to select left, right or ahead directions. One set of routes was unique, whereas another set contained overlapping corridors, such that although the starting point was unique, either a second or third corridor would overlap with another route. At the choice point following the overlapping corridor, one route would require a different (left, right or ahead) choice relative to another.

The predictions were that where the same corridor required a different route choice, depending on the route context set by the starting corridor, there would be greater hippocampal and caudate activation (Brown et al., 2010), and that there would be higher levels of connectivity between hippocampus and caudate on overlapping versus non-overlapping routes (Brown et al., 2012), when contrasting activations in the critical overlapping hallways, with their equivalent non-overlapping counterparts. It was also predicted that there may be more hippocampal activity in the first hallway of overlapping versus non-overlapping routes, as a form of prospective memory for anticipating the correct route. Results supported these predictions, and similar results were obtained for newly overlapping routes (Brown & Stern, 2014) as for well-learned overlapping routes (Brown et al., 2010; 2014), suggesting both learning and performance involve collaboration between hippocampus and caudate, as predicted by theory emphasising collaboration between hippocampus and caudate as part of an associative cortico-basal ganglia loop (Yin & Knowlton, 2006).

Given evidence such as that from the work of Brown and colleagues (Brown et al., 2010; 2012; Brown & Stern, 2014) the question arises as to how to reconcile results with the earlier fMRI evidence, finding competitive interactions between hippocampus and caudate (Hartley et al., 2003; Doeller et al., 2008; Marchette et al.,

2011; Wegman et al., 2014). One potential issue arises with the focus on performance-related correlations, some form of which are used by most of these studies (Hartley et al., 2003; Doeller et al., 2008; Marchette et al., 2011). It may be expected that situations which generate response conflict will give rise to higher caudate activation, if this area is involved in selecting between competing action "bids". Thus in the study by Hartley et al. (2003) for instance, it is possible that poor navigators experienced more response conflict in the way-finding task requiring a map-like representation of the environment, therefore showing more caudate activation relative to good navigators. Conversely, the good navigators that showed higher caudate activation in the route-following task relative to poor navigators, were doing so because they were experiencing more response conflict in terms of wanting to take shortcuts, or exploratory routes, as opposed to sticking with the prescribed route. Such spatial exploratory behaviours were evidenced in the Marchette et al. (2011) study by good navigators, who spontaneously, without instruction, noticed potential short-cuts during the passive encoding of the prescribed route, which they then used in the retrieval phase of the experiment. This account provides an alternative to the suggestion made in Hartley et al. that good navigators select the appropriate system, hippocampal or striatal, for a novel shortcuts task versus a prescribed route task. This alternative interpretation is more consistent with reformulations of parallel memory systems theory (Yin & Knowlton, 2006).

Only one study found differences in activation between conditions involving encoding a landmark-to-goal vector versus encoding a goal location with respect to a constellation of three landmarks (Wegman et al., 2014), as opposed to reporting performance-related effects. In this study, during encoding the goal location was marked in relation to a constellation of three landmarks, with direction provided by

shadow effects on each landmark. During goal retrieval, either a single, shadowed landmark was present, or two out of the three landmarks, with no shadow information. During encoding, the single landmark to be present during retrieval was cued in single-landmark trials, versus only one of the two possible landmarks being cued in two-landmark array trials. Thus it is possible that more movement planning could take place during encoding in single landmark trials, versus landmark array trials, perhaps leading to the higher caudate activation observed in single landmark trials.

The preceding discussion highlights the difficulty of matching fMRI findings clearly onto different models of striatal function. It could be argued that fMRI studies should focus on putamen activation, as being a region more associated with sensorimotor striatum, and therefore stimulus-response and habit learning, in order to address predictions arising from parallel memory systems theory about the function of this region. This presents challenges however, in that most tasks that involve any kind of reward-related motor response are likely to activate the putamen (see discussions in Patterson & Knowlton, 2018 and Woolley, Laeremans, Gantois, Mantini, Vermaercke, Op de Beeck et al., 2013).

In following sections, a final version of parallel memory systems proposed by Khamassi and Humphries (2012), developing further the division of function within the striatum into types of learning algorithms, will be reviewed, together with subsections on relevant non-human lesional and human fMRI evidence, prior to the rationale for the present research. These proposals can be considered an extension of the Yin and Knowlton (2006) review, giving a formal account of what flexible, associative cortico-striatal loop, task performance entails. The basis of the Khamassi and Humphries proposal comes from work within the field of neurocomputation

(Bornstein & Daw, 2011; Daw, Niv & Dayan, 2005) and machine reinforcement learning (Sutton & Barto, 1998).

Model-free versus Model-Based Learning Accounts of Parallel Spatial Memory Systems: Khamassi & Humphries (2012)

The work of Sutton and Barto (1998) developed computational tools for implementing reinforcement learning. These tools involved conceptualising tasks as consisting of states of the world, where a set of possible actions are available. The process of action selection is guided by a reward prediction function associated with each action choice, as well as a general reward prediction associated with each state. This reward prediction function can be altered during learning by "critic" units in the model computing the difference between predicted and actual reward. This difference can be used to alter the reward value associated with both the selected action, as well as the state preceding the action overall (which can be expressed as a weighted sum of the reward value across all possible actions in that state). Each action leads to a new state or context, where the process of action selection can take place again, until a goal state is reached, or an alternative unrewarded end-point.

In most natural and laboratory tasks, reward (such as food) only occurs at an end state of a series of actions. The conceptual breakthrough in terms of developing learning algorithms given this reality, is to have the teacher signal from the critic after a transition from one unrewarded state to another given by the magnitude of a predicted reward function; thus not only is primary reward after action selection being predicted, but the reward prediction value of the state that will be entered after action selection has occurred. Such a type of learning rule has been demonstrated to be able to learn a series of actions to reach a rewarded goal, via initial exploratory trial-and-error discovery of the correct action sequence (Barto, 1995; Sutton & Barto, 1998).

This is because the first time the primary reward is discovered, the reward prediction of the preceding state will be altered in a positive direction, making it more likely that the correct action choice will be made in following trials when that immediately preceding state is encountered. Through repeated trials, the positive reward prediction will be propagated backwards to earlier action steps and states, until the agent is able to reliably perform the correct sequence of actions. Only the selected action is eligible for change in terms of the strength of its association with a particular state, depending on the difference between the actual versus predicted reward value of the state occurring after the selected action has taken place. If the prediction was accurate, no change in weights is made, whereas if the prediction undervalued the reward prediction associated with the state after action selection, a strengthening of preceding state-action weights occurs (or a decrease if the reward prediction was higher than the actual reward prediction of the post selected action state). Such types of learning rules have collectively been termed "model-free", in the sense that there is no explicit representation of the action steps leading to the reward; rather each state-action pairing reflects the average reward associated with that particular action, relative to other possible actions in that state, following learning experiences.

In contrast to such model-free learning algorithms, model-based learning rules do explicitly represent a sequence of actions, which may or may not lead to primary rewards. While computationally demanding in terms of memory storage, such representations allow action decisions in particular states to be made on the basis of past chains of linked actions and states of the environment, usually conceptualised as action-outcome chains. As with model-free algorithms, during learning, the values of actions are still learnt using both the reward obtained following action (if present) and the value of the reward prediction function in the state following the action, i.e. with

learning occurring if prediction was inaccurate prior to action selection. However, a forward search through the values associated with possible chains of future actions is permitted prior to action selection, and outcomes of actions are represented.

Model-free and model-based algorithms (Sutton & Barto, 1998) have not only transformed machine learning fields of application and research, but they have also influenced conceptualisations of brain function, with emphasis on the basal ganglia (Barto, 1995; Bornstein & Daw, 2011; Daw et al, 2005; Khamassi & Humphries, 2012; Pennartz et al., 2011; Yin & Knowlton, 2006). In particular, dopaminergic systems within ventral striatum have been hypothesised to perform a critic role in reinforcement learning (review in Bornstein & Daw, 2011), as have dopaminergic systems within striosomes within dorsal striatum, where striosome compartments form approximately 20% of tissue, relative to 80% matrix compartments (striosome and matrix compartments are defined by neurochemical markers; Graybiel & Moratalla, 1989; Khamassi & Humphries, 2012; Pennartz et al., 2011; Shipp, 2017). Matrix compartments of dorsal striatum have been associated with the actor role in reinforcement learning (Khamassi & Humphries, 2012; Pennartz et al., 2011; Shipp, 2017). Bornstein and Daw (2011; also Daw et al., 2005) further proposed a mapping between dorsolateral striatum as underpinning model-free learning and action selection, with dorsomedial striatum collaborating with hippocampal and medial prefrontal areas to support model-based systems. These authors argued that the two systems are necessary in the trade-off between computational simplicity in more automatic decision-making, and flexible but computationally demanding decision-making. Prefrontal systems are hypothesised to arbitrate in action selection when the two systems provide differing action “bids”.

Khamassi and Humphries (2012) used the framework of Bornstein and Daw to reconsider the spatial navigation literature on parallel memory systems. In particular, they argued that while traditional formulations based on stimulus-response associations to single cues, or "snapshots" (dorsolateral striato-cortical loops), versus flexible use of cognitive maps (dorsomedial striato-cortical loops) appear to map on to model-free and model-based learning systems respectively, the difference lies in the emphasis on type of learning rather than type of cue to distinguish the parallel systems. The authors analyse the results from several lesional studies using tasks that appear to only require stimulus-response associations in terms of spatial information, that nevertheless show sensitivity to dorsomedial striatal or hippocampal lesions. When these studies are examined from the point of view of the type of learning required for task solution however, the lesional data are consistent. These studies are reviewed in the following section.

Non-human lesional studies.

Moussa and colleagues (Moussa, Poucet, Amalric & Sargolini, 2011) carried out a study using a continuous alternating T-maze paradigm, where rats were required to run from the start point up the central arm, before making a right or left turn to reach an appetitive reward at the end of the T arm. A correct response involves a return to the start via a diagonal runway from the reward site to the start location, followed by a trial now involving a turn opposite to the turn made on the previous trial at the T-junction. The apparatus was set within a cue-rich environment. Under a response versus place dichotomy in terms of parallel systems, such a task could be considered an extension of a response task, in that a prescribed route can be followed for successful performance. Therefore, lesions of dorsomedial striatum would not necessarily impair performance on such a task. Using dorsolateral striatum,

dorsomedial striatum and sham lesion groups, Moussa et al. (2011) found that rats with dorsomedial lesions were impaired, relative to sham and dorsolateral striatum groups, in both their rate of task acquisition and final levels of performance at asymptote. The sham and dorsolateral striatum groups did not differ from each other in terms of final performance, although the dorsolateral lesion group showed faster learning than the sham group. Finally, during 10 minutes of unrewarded exposure to the apparatus at the end of the experiment, rats with dorsolateral striatal lesions showed faster extinction of correct responding relative to the other two groups.

Khamassi and Humphries (2012) argued that the results of Moussa et al. (2011) could be accounted for by considering that a model-free learning system would have difficulties with the alternating T-maze task, because both left and right responses at the end of the central arm will have been rewarded an approximately equal number of times, therefore action selection based purely on cached stimulus-action reward values would not yield successful performance. A minimal model is required to solve the task, according to this view, based on the need for a conditional response at the end of the central arm of the T, depending on the memory of the previous response. Thus dorsomedial striatal lesions cause task impairment due to impairment in model-based action selection. In addition, the parallel action of model-free and model-based learning is evidenced by the faster extinction demonstrated by the dorsolateral lesion group, relative to shams and dorsomedial lesion groups. This is because without competition from the model-free learning system, both learning of the task contingencies can occur at a faster rate, and so can outcome-sensitive extinction.

The converse claim to the suggestion that some model-based tasks involve egocentric responses, is that some model-free tasks involve (hippocampus-dependent)

place responses. Khamassi and Humphries (2012) interpret data from a series of studies by Frank and colleagues (Jadhav, Kemere, German & Frank, 2012; Kim & Frank, 2009) as evidence for such a claim. Kim and Frank (2009) used a continuous alternation W-maze task to examine the effects of hippocampal lesions on different types of memory requirements within the same task. The W-maze consists of 3 alleyways in which a food delivery well is found at the end of each alleyway. A further alleyway perpendicular to the entrances of the rewarded alleyways connects the three alleyways (forming the rectangular W shape), permitting free movements between all arms of the maze. The task consists of obtaining food reward at the end of the centre arm (away from connecting alleyway), and then visiting either the right or left alleyway for further reward. A return visit to the centre is then required, prior to a visit to the opposite side arm to that carried out on the last outer alleyway visit (i.e. Centre, Left, Centre, Right, or Centre, Right, Centre, Left). Pre-training hippocampal lesions impaired learning of both the inward (towards the centre) and outward (towards the left or right) alleyways (Kim & Frank, 2009), whereas disruption of hippocampal sharp-wave ripples during task performance in otherwise intact rats only disrupted outward trial performance (Jadhav et al., 2012). These sharp wave ripples are associated with pre-play/re-play phenomena in hippocampus whereby previous sequences of actions are neurally re-enacted (Foster & Wilson, 2006).

Khamassi and Humphries (2012) argued that the hippocampal system fed place information to both model-free (dorsolateral striatum) and model-based (dorsomedial striatum) systems in the W-maze task. The association of turning towards the centre when located at the top of the left-most or right-most alley can be learnt by a model-free system, given intact place information (e.g. two different state-action transitions). However, using the same logic as in their analysis of T-maze

alternation performance in Moussa et al. (2011), the appropriate turn to make at the top of the centre alley requires a model-based learning system, in that the correct turn is based on the prior context (whether a left or right alleyway was visited), with a model-free system facing uncertainty due to the approximately 50% reward levels accrued with either left or right turns over the course of experience. According to this view, hippocampal lesions affect performance in both inward journeys to the centre arm of the W-maze, and outward journeys to left or right arms, because place information is impaired, signalling the rat's current state (Kim & Frank, 2009). However, interference with on-line replay of prior action sequences (Jadhav et al., 2012) affects only on-line model-based decision making, rather than place recognition, leading to impaired performance on outward journeys only.

The evidence that use of response sequences in action selection requires dorsomedial striatum/hippocampal interactions appears clearer than evidence that true place information reaches dorsolateral striatum. In the Kim and Frank (2009) study, cue information provided by the W-maze itself (rather than use of configurations of distal laboratory cues providing place information) could have provided current state or context information, i.e. whether a corner had an outer wall to the left or right of the rat, or whether a T-junction shape (as at the top of the centre arm) was present. Additionally, lesioned rats did learn to carry out inbound trials to criterion after approximately 7 days, generally after overcoming a perseverative tendency to run from side to side, without entering the centre arm of the W-maze. Kim and Frank (2009) discuss whether the hippocampal lesions were having their effect on inbound trials through a failure of inhibition of a previously acquired response which involved shuttling back and forth on a straight track during pre- and post-lesion pre-training. In contrast, although half the lesioned rats were eventually able to reach criterion

performance on outbound trials (i.e. after correct visits to the centre alleyway), half did not reach criterion, suggesting a more lasting impairment in being able to use the memory of their previous behaviour to guide decision-making.

Khamassi and Humphries (2012) raise several open questions in relation to evidence for their model. The first is how place information reaches the dorsolateral striatum, given the lack of direct connections between hippocampus or medial prefrontal cortex and dorsolateral striatum, in contrast to the presence of such connectivity with dorsomedial striatum. Additionally, they acknowledge the similarity across striatal territories and thalamocortical striatal loops in terms of microcircuitry, ideally suited for response selection (and inhibition) based on learned reward values and state information (Lau, Monteiro & Paton, 2017; Pennartz et al., 2011; Shipp, 2017). There is also emerging evidence that the same dopamine neurons in basal ganglia nuclei that show reward prediction errors consistent with a model-free learning "critic" role, also show more context-dependent responses under particular task conditions, again pointing to commonality of learning mechanisms (Lau et al., 2017; Pennartz et al., 2011). Khamassi and Humphries suggest that the distinction between the proposed dorsolateral and dorsomedial striatal model-free and model-based systems may be driven by the provision of hippocampal and prefrontal cortical input to the latter providing state-transition information. In contrast, the sensorimotor and premotor cortices, together with higher level sensory areas, may provide state information to dorsolateral striatum. Thus it is not necessary to posit different classes of dopaminergic neurons to each system, underpinning different types of reward learning; rather, the nature of the information available to each system determines model-free versus model-based learning.

The argument of commonality of learning mechanisms is further developed by Pennartz et al. (2011) who suggest that all parts of the striatum (dorsolateral, dorsomedial and ventral) may be involved in outcome prediction (associated with model-based learning), therefore aiding response selection, but across different informational domains. Dorsolateral striatum may be involved in predicting the next motor action or sensorimotor input, relative to dorsomedial striatum predicting the what and where of an outcome. Such a scheme is consistent with the suggestions of Smith and Graybiel (2016), reviewed above, that dorsolateral striatum has a role in outcome prediction and habitual automaticity, as opposed to showing clear stimulus-response correlates at the level of cellular neurophysiological recordings. Dezfouli and Ballaine (2012) go further still by suggesting that action chunking in and of itself is a better explanation for the resistance of habitual behaviour to reward contingency change, as opposed to suggesting that model-free learning algorithms underpin such phenomena. This is because changes in action-outcome contingencies within an automatized chunk have lost their individual flexibility, in favour of start and end elements of the chunked sequence. These alternative proposals for dorsolateral striatal function will also be considered further in the rationale for the proposed research.

Although Khamassi and Humphries do not consider fMRI studies addressing division of function between dorsolateral and dorsomedial striatum, in the following section the work of Igloi and colleagues (Igloi, Doeller, Berthoz, Rondi-Reig & Burgess, 2010) will be reviewed, as it appears to fit well within the scheme of emphasising type of learning as the key feature of which tasks will be hippocampus-dependent, over and above the place versus response dichotomy. The work of Igloi and colleagues was based on a study by Rondi-Reig and colleagues with knock-out mice with impaired hippocampal function, due to lack of NMDA receptors, where

mice were unable to learn to make a sequence of turns (e.g. left, right, left) to reach an escape platform in a star-shaped maze with 5 radiating alleys emanating from the corners of a pentagon-shaped central alleyway (Rondi-Reig, Petit, Tobin, Tonegawa, Mariani & Berthoz, 2006). Interestingly, mice were able to negotiate the first junction with above chance performance, but performed at chance levels at the following junctions. Within the Khamassi and Humphries (2012) framework, although not discussed by these authors, the Rondi-Reig et al. (2006) results could be accounted for by the need for a functional hippocampus to support a model-based learning system, so that similar looking junctions can be distinguished though memory of previous choices.

Human fMRI studies.

Igloi and colleagues (Igloi et al., 2010) constructed a radiating starmaze virtual environment, following the design of Rondi-Reig et al. (2006), reviewed above. Participants learnt to find a goal at the end of one arm of the starmaze by negotiating 3 junctions (left, right, left). There were distinctive distal landmarks at the end of each arm of the star maze. However, during probe trials, participants (without warning) were placed in a different starting arm, one of which had rather similar distal landmarks to the usual starting arm, whereas the other had differing landmarks. Most participants repeated their usual sequence of turns during probes with the similar view, often correcting themselves halfway along the trajectory. During the probe trials with the differing view, participants generally took the appropriate novel route to reach the goal location. A set of control trials consisted of participants navigating the starmaze with no landmarks, and with barriers at choice points forcing them to take a particular route.

In order to compare different probes with control trials, as well as each other, contrasts were made for the first path only, capturing route planning processes. There was greater right hippocampal activation relative to control trials in different view probes, as would be predicted given that a novel route is required based on an allocentric representation of the goal location. Consistent with Rondi-Reig et al. (2006), there was greater hippocampal activation relative to control trials in similar view probe trials, although interestingly this was higher for left relative to right hippocampus (see also Babayan, Watilliaux, Viejo, Paradis, Girard & Rondi-Reig, 2017 for a study showing coherence of hippocampal and cerebellar c-Fos expression in mice during egocentric-sequential navigation). This hippocampal involvement in the sequential egocentric route probe would not be predicted in traditional formulations of parallel systems theory, where following a prescribed route would be considered a striatal systems task. It is consistent with the view that in order to disambiguate rather similar junctions, a model-based system utilising the hippocampus is required (Khamassi & Humphries, 2012). However, given parallel information flow into both hippocampal and striatal systems, clear predictions in terms of differences in BOLD signal correlated with function are problematic, as discussed earlier.

In terms of striatal activations, both egocentric sequential and allocentric probe trials showed higher caudate and ventral striatum (nucleus accumbens) activations relative to control trials, with no differences in these areas in the sequential egocentric versus allocentric probes contrast. These findings are consistent with a perspective that views hippocampal and caudate activations as part of a collaborative network serving to guide action selection through model-based decision making, although such models were not being tested in the study of Igloi et al. (2010).

It should also be noted that the results of Brown and colleagues (Brown et al., 2010; 2012; 2014) in their overlapping versus non-overlapping routes study are consistent with the perspective of hippocampal-caudate interactions being necessary for model-based decision-making, although again, these authors do not explicitly discuss such models.

From the preceding review, it is clear that a reappraisal of the mechanisms supporting complex route-following is required. While in principle, such route following can be accomplished by a set of learned stimulus-response pairings between landmarks and actions at key junctions, as envisaged by classical parallel spatial memory systems theory (Hartley et al., 2003; O'Keefe & Nadel, 1978; White & McDondald, 2002), in practice several parallel mechanisms may interact, cooperatively and/or competitively, in route learning. As well as the learning of the individual stimulus-response associations, irrespective of the sequence of junctions, classically associated with dorsolateral striatum in the neurobiological literature (White & McDonald, 2002), the actual sequence of landmarks, and landmark-actions, can be learned. The sequence of landmarks encountered in the route, and either independently or in interaction, the sequence of egocentric movements involved in the route, could be learned by hippocampal systems in interaction with dorsomedial (caudate) striatum, perhaps together with other brain systems such as the cerebellum (Babayan et al., 2017; Igloi et al., 2010, Rondi-Reig et al., 2006). When such sequences become habitual, dorsolateral (putamen) involvement may control behaviour (Dezfouli and Ballaine, 2012; Smith & Graybiel, 2016).

Rationale for the Present Research

In the present research, we seek to exploit the parallel learning of individual landmark-action associations and sequence knowledge that occurs in complex route-

following, in order to reveal the brain systems underpinning each of these types of learning. Participants learn a 9-junction route through a virtual environment and navigate this route, or segments of it, together with a set of probe and control trials, while undergoing fMRI. Distinctive landmarks are present at each junction of the route, thus allowing both the learning of individual landmark-action associations, as well as the sequence of landmarks and egocentric turns forming the route.

In order to distinguish systems involved in performing a response based on landmark-action associations, versus a response based on sequence knowledge, short probe trials are presented in which a landmark is presented out of sequence, such that if the participant responds on the basis of the individual landmark-action association they would make an opposite response (e.g. left instead of right) to the one they have learned to make at that junction. Thus on these conflict probes, participants can be divided into landmark-based responders and sequence-based responders. Under a classical parallel spatial memory systems view (White & McDonald, 2002), both these types of responses would be considered to be under the control of striatal systems, with little distinction made between them. Based on a view distinguishing model-free and model-based learning (Khamassi & Humphries, 2012), it would be predicted that sequence responders would show greater hippocampal activations relative to landmark responders, and also relative to control probes, as they have to base their route decision on their previous trajectory, together with their acquired route sequence knowledge. It would also be predicted that there would be greater connectivity between hippocampus and caudate in sequence responders, as knowledge of the previously traversed route would have to be utilized to make a sequence response (Brown et al., 2012). Following Igloi et al. (2010), control probes involve navigation through the route with no landmarks and a junction blocked by a

fence, such that the participant navigates a similar path, but does not have to use route knowledge to make decisions at junctions.

While it could be argued that landmark responders should show greater putamen activations relative to control probes, based on the lesional evidence reviewed above for the involvement of the dorsolateral striatum in stimulus-response learning, there are very few fMRI studies within the navigation literature that report task-related putamen activations (although see Wegman et al., 2014). Thus although hippocampus, caudate and putamen are examined in all contrasts as predefined regions of interest (ROIs), together with whole brain contrasts, these will be treated as exploratory for landmark responders versus control probes contrasts in terms of putamen activations. A recent meta-analysis of spatial imaging studies (Cona & Scarpazza, 2019) has found that parahippocamal areas are more reliably activated in diverse spatial tasks that the hippocampus itself. Because this work was not available at the final design stage of the present research, and also because predictions are based on the findings of Igloi et al. (2010) in terms of hippocampal activations, we do not treat parahippocampal cortex as a predefined ROI; however we do widen our perspective in terms of predictions to include the hippocampal formation, with respect to being associated with model-based processing. In addition to hippocampal formation activation, it may be expected that whatever the response produced in conflict probes, there should be increased caudate activation relative to control probes, in that more response conflict is generated in conflict probes.

A second type of short probe, sequence probes, that will be investigated involves navigation through a segment of the route where a landmark is unexpectedly absent. In this situation, it is expected that hippocampal formation activity, in collaboration with caudate, will be required to generate the correct response, as

knowledge of landmark sequence is required. Thus there should be higher hippocampal and caudate activation in sequence probes relative to controls, as well as greater connectivity between these areas.

Following four runs of trials where short probe trials (conflict probes, sequence probes and control probes) are interspersed with full and partial route navigation trials, 4 final runs of trials with different probes will be presented. In these final blocks, participants are alerted that they will either have to traverse a set of junctions where only landmark-action knowledge will be useful, because junctions are presented in random order, or, conversely, after an initial junction with a landmark, they will be required to navigate the following junctions based solely on memory for the route sequence. Each run contains 6 alternating sets of trials, 3 landmark trials, and 3 sequence trials, where each trial contains 3 junctions, with the sequence trials starting at different points along the learned route.

The rationale for these long-probe runs is two-fold. Firstly, these long-probes explicitly access either individual landmark or sequence knowledge, so participants are forced in their strategy use, unlike the conflict short probes described above, where they can spontaneously select equally valid landmark- and sequence-based strategies. Secondly, the first paths of these probes could be particularly informative, in that they are identical in featuring a landmark along the route. However, in the long sequence probes, the landmark should trigger a route-planning process, as the participant knows there will be no further landmarks to guide them along subsequent elements of the route. This planning process should be absent in the long landmark probe, where landmark order is random. In terms of predictions, both the classical parallel systems perspective (Pistell et al., 2009), and views of dorsolateral (putamen) function that emphasise action sequencing (Dezfouli & Ballaine, 2012; Patterson &

Knowlton, 2018) may predict that there should be greater putamen activity in the first path of long sequence probes, relative to long landmark probes, due to sequence planning having become automated. Alternatively, greater hippocampal and caudate activity may be predicted (Khamassi & Humphries, 2012), due to use of a model-based strategy to predict subsequent correct choice based on the context-setting initial landmark, as outlined above for sequence-based responses during unexpected short probes.

Due to time-constraints, only the univariate contrasts are reported in this thesis, with planned connectivity analyses referred to as appropriate within the Discussion section.

Chapter 2: Method

Participants

A total of 27 participants (18 females and 9 males; mean age 23.6 years, range 19-34 years) gave signed consent and were paid for participation in the study. The study was approved by the Ethics Sub-Committee of the Experimental Psychology Department at Durham University. The data from 2 participants was excluded due to excessive head movement, and signal loss occurred in a further participant, leaving a final sample size of 24 (16 females and 8 males).

Virtual Environment Design

A 9-junction route in a virtual environment (VE) was constructed using Unity 2017.4.2f2 (https://unity3d.com/). Figure 1 shows a plan view of the route, and screenshots displaying the first person perspective at the beginning and end of route junctions. The overall task of participants was to learn to navigate the route without errors. Junctions consisted of a 2-choice Y-junction where left and right button-presses controlled left and right junction choices respectively. Participants were moved passively along each path for 2.5 s at a speed of 2.9 vm/s, with a field of view of 55°, and viewing height of 1.7 vm. A unique landmark was placed at each junction i.e. windmill, bench, sundial, chimenea, fountain, composter, well, birdhouse and birdbath. Once participants arrived at a junction, two black arrows along the left and right paths signalled that a response could be made. Participants selected their left or right choice without being able to rotate their field of view to observe any landmarks beyond their current junction. On reaching the goal location, a garden house, at the

end of the route, fireworks were displayed for 2.5 s.

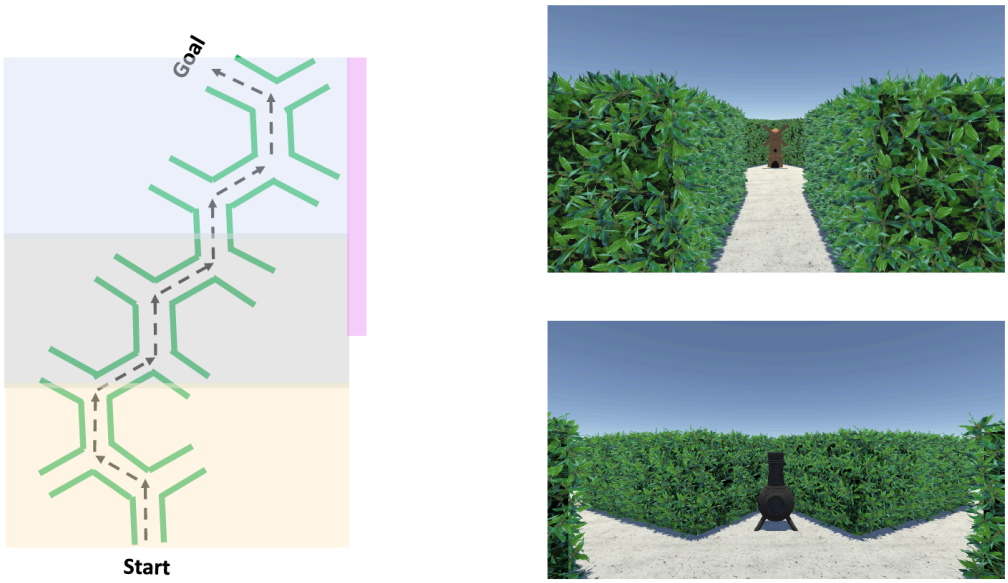

Figure 1. Plane view of the VE route (left) and first person view of pathways and junctions (right). See text for further details.

If participants made a correct response at a junction, they experienced a passive rotation of 60° degrees before movement along the path towards the next junction. If an incorrect response was made, the rotation occurred, and a potted plant was visible along the incorrect path, prior to a red mist obscuring view (total duration of feedback procedure 4.5s), with the participant being returned to the original junction where they were able to make the correct choice.

As well as experiencing trials involving traversing the full route, various other types of trials were presented, at different phases of the experiment, as described in the following section. All route choices and reaction time data at junctions was recorded using Unity 2017.4.2f2, together with timestamps for all events within a trial.

Experimental Protocol

Pre-scan training. On the day prior to scanning, participants learnt the route through the VE in a training task lasting approximately 15 mins (see Appendix A for text of instructions to participants in all phases of the experiment). Initially, the task consisted of trials traversing the whole route, with incorrect choices being subject to feedback, until the participant completed two consecutive trials with no errors. The inter-trial interval used throughout the training was 6 seconds during which a blank screen was displayed. This pre-scan training was conducted in the mock scanner based at the Experimental Psychology Department, Durham University, in order to acclimatise participants to the scanning environment.

Once criterion performance of 2 consecutive error-free trials had been reached, a pseudo-randomised set of 5 different trial-types were presented 4 times each (i.e. a total of 20 trials), such that the same trial type was not presented consecutively. Three of the 5 different trial types consisted of shorter route segments, where only 3 junctions of the route were presented; once the participant had made their 3rd choice, they travelled down the 4th path for the usual 2.5s, but the screen then faded to black signalling the end of the trial, if they were not at the end of the route. The colour blocks of figure 1 show these route segments, starting at the windmill (yellow), chimenea (grey) and well (blue). The short route training starting at the well led to the garden house and ended with the fireworks reward, as in the full route trials, rather than fading to black.

The purpose of these shorter route segment training trials was two-fold. In terms of learning the individual landmark-action associations comprising the route, they were important in preventing some participants learning the full route as a verbal list of 9 right/left turns, without any learning of landmark-action associations.

Because 2 of these shorter routes did not start at the beginning of the route, they ensured that such a verbal strategy was ineffective. The other function of these shorter training segments was to prepare participants for probe trials in the part of the experiment that was conducted within the fMRI scanner, detailed below.

A longer, 5-junction route trial, ending in reward was also presented, starting at the fountain, indicated by the thin purple segment in Figure 1 (left). The purpose of this trial type was to have a trial that started in the first half of the route, but still led to reward, thus avoiding the possibility that participants would associate trials starting relatively early on in the route with termination without reward. Finally, the full route was also presented. Thus the 3-junction routes, the single 5-junction route and the full route formed the 5 different trial types presented for 20 trials during training. Following the training in the VE, recognition memory for the route was assessed by asking participants to order screenshots of the landmarks in the correct order. Participants then carried out a set of 4 pen-and-paper individual differences measures relating to spatial navigation abilities. This data is not considered further in this thesis due to time constraints.

On the day following pre-scanning training, participants had the opportunity to refresh their knowledge of the full route prior to the scanning session, by conducting trials in the VE traversing the whole learned route, to a criterion of 2 errorless trials. Only three participants made an error, thus taking 3 trials to reach criterion, with the remainder taking the minimum of 2 trials, suggesting the route was well learned prior to scanning.

Neuroimaging task. Trials were presented to participants in 9 runs while fMRI data was collected. Experimental stimuli were presented on an MRI-compatible monitor viewed through a mirror mounted on the MRI head coil. Participants used an

MRI-compatible response box to indicate choices at each junction. The first run consisted of a training phase in which participants again had to reach a criterion of two errorless trials in the full route before proceeding. All but one participant achieved this in the minimum of 2 trials, with one participant requiring 3 trials. There ensued a pseudo-random set of the same trial types as described in the previous section, with 2 trials of each type of route. Additionally, 6 control trials were interspersed with these training trials, modelled on control trials used by Igloi et al. (2010). These consisted of the same 3-junction routes as were used for pre-scan training (see Figure 1, left; yellow, grey and blue route segments), each presented twice, but with no landmarks present, and barriers (wooden fence units) blocking access to one of the junctions. At the beginning of the run, participants were alerted to the possibility of routes where paths were blocked, and they were instructed to select the available path (see Appendix A for full instructions). For this run and all subsequent runs, a jittered inter-trial interval of 4s ±2s was utilized, followed by a 2s white central fixation cross on a black background to alert the participant to the start of the next trial.

A second phase of the experiment followed after the training run, the short probes phase, and consisted of 4 scanning runs. Each run consisted of 24 trials. Participants were instructed that they would be presented with trials they were familiar with, and also some where something might have changed. In such cases there would be no feedback as to whether their responses were correct or not, but they should respond guided by the knowledge that the learned route to the garden house remained unchanged (see Appendix A for full instructions).

Eighteen of the 24 trials consisted of probe trials, with three different types of probe presented (Figure 2). There were 6 short sequence probe trials, where after an

initial junction, the following junction had no landmark. Therefore, the participant had a choice of making a response based on the correct sequence e.g. a left turn in the top panel of Figure 2, or they could make an incorrect response. The six sequence probe trials were made up of 2 repetitions of the 3 short route segments depicted in Figure 2. There were 6 short conflict probes whereby a second junction contained an out-of-place landmark, giving rise to a conflict between a sequence response, in which the participant makes a turn based on the usual sequence encountered on the learned route, or a landmark response, based on the individual learned landmark-action association, now in conflict with a sequence-based response. In the top panel of Figure 2, a left turn usually follows after the well, whereas a right turn is usually associated with the fountain, in the learned route. As with sequence probes, each of the route segments displayed in Figure 2 was presented twice in each run. Finally, six, 2-path control probes were presented, constructed of the same path segments as depicted in Figure 2, but with no landmarks and a barrier fence blocking access to one of the arms of the junctions. Three of these control segments followed the path of a sequence-based response, and three followed the path of a landmark-based response.

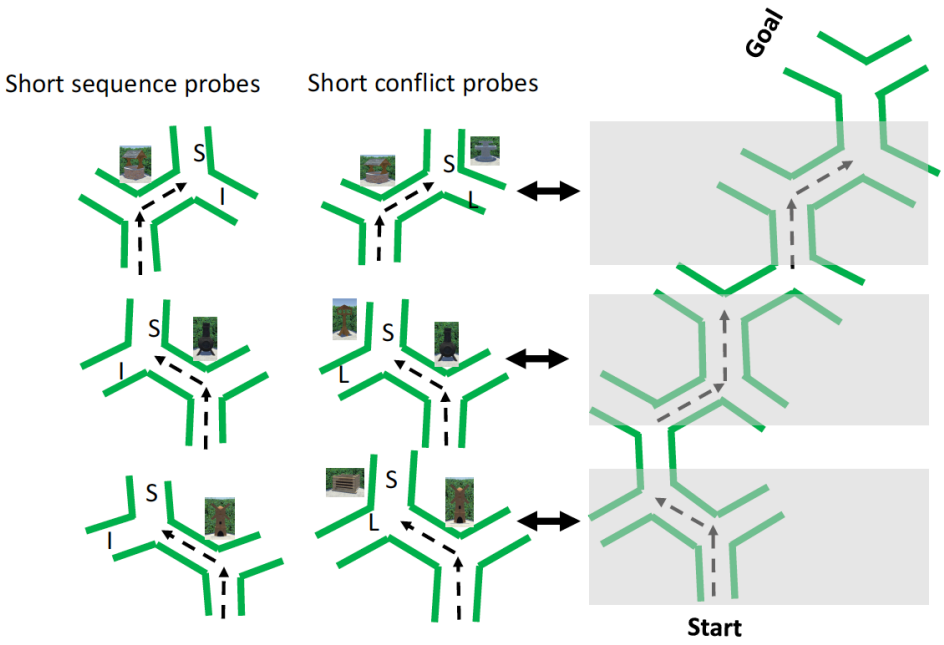

Figure 2. Plane view of different types of short probes utilised in the 4 runs of short probe runs. S = a sequence-based response, L = a landmark-based response and I = an incorrect response. The double-headed arrows indicate the path segment from the whole route from which the short probe trial is derived.

The probes were presented in 6 groups of 3 (in random order). Before each group of 3, one type of training trial would be presented to refresh the route, and make trial type unpredictable. There were 6 of these training trials, one full route trial, one of each of the 4 shorter segments presented in Figure 1, and finally one training control trial. The order of the training and probe trial types was pseudo-randomised. In total, this design yielded 24 probe trials of each type for each participant, for entry into analysis.

A final, long probes phase of the experiment was presented in 4 scanning runs. Each run contained 6 long probe trials, which were formed of three long sequence probes and three long landmark probes, presented in alternating order, counterbalanced across participants in each run. Thus there were 12 sequence long probes and 12 landmark long probes in total for each participant. A long sequence

probe consisted of one of the 3, 3-path segments displayed in the colour blocks of Figure 1, with only the first landmark present, with subsequent junctions having no landmarks. A long landmark probe consisted of 3-path segments where landmarks occurred in random order. Participants were provided with an explanation prior to the commencement of the run as to the form each type of long probe would take (see Appendix A for instructions), and then during scanning, a label signaling whether an up-coming probe required landmark or sequence responses was provided for 4 s on-screen, before the fixation cross signaling the start of that trial occurred.

After scanning, participants were debriefed and provided with an opportunity to ask questions if they wished.

Image Acquisition

Imaging data were acquired at the James Cook University Hospital, Middlesbrough, using a 3 T Siemens Magnetom Trio scanner with a 32-channel Tim matrix head coil. Functional T2*-weighted BOLD images were acquired using an axial echo planar imaging sequence of the whole brain (repetition time, TR, 2000 ms; echo time, TE, 62 ms; gap 0.3 mm, flip angle, 90°; acquisition matrix, 96 x 96; field of view, 210 x 210 mm, slices, 32; resolution 3 x 3 x 3 mm). Slices were acquired in the sagittal plane in ascending interleaved order. The 4th run out of a total of 10 in the experiment consisted of a high-resolution T1-weighted anatomical scan using a multiplanar rapidly acquired gradient echo sequence (TR, 2250 ms; TE 2.52 ms; no gap; flip angle, 9°; acquisition matrix, 1024 x 1024; field of view; 512 x 512 mm, slices, 192, resolution 1 x 0.5 x 0.5 mm). The first 3-5 slices were discarded for all runs to allow for stabilization of images.

fMRI Pre-Processing

Imaging analysis was conducted using BrainVoyager 20.2 (Brain Innovation, Maastricht, The Netherlands; Goebel, Esposito & Formisano, 2006). Functional images were slice time corrected to the first slice, high-pass filtered (0.006 Hz), and 3D motion corrected with a trilinear interpolation. The functional images were co-registered with the structural scans for each participant, and were then spatially normalized onto AC-PC Talariach space (1 x 1 x 1 mm). The resulting volume time courses were smoothed using a 6 mm full-width at half-maximum Gaussian kernel.

Data Analysis

Behavioural analysis. Accuracy data was collated to ensure participants were making predominantly correct responses in short sequence probes, as well as in the long landmark and sequence probes. If any participant failed to show a majority of correct probes, they were excluded from analyses, although checks were made on whether results were altered by these exclusions, with these checks referred to in the relevant results section. Further individual binomial tests (with a $p < 0.05$ threshold) were run to check that participants were significantly above chance in their correct responding, as well as showing a majority of correct trials. If any participant failed to reach this above chance threshold, their data was included in relevant contrasts for fMRI data, but checks were run to ensure that results were not altered by their inclusion. For conflict short probes, participants were classified into sequence responders or landmark responders, based on their majority response across their 24 trials. Binomial tests for each participant were conducted to check that this majority response was above chance. For any participants that failed this threshold, checks were made that excluding their data from the relevant fMRI contrasts did not alter results.

Reaction time (RT) data was collated for the probe trials forming the relevant contrasts in the fMRI analyses, detailed below, and were analysed using ANOVAs, to check whether reaction time needed to be included as a potential confound in fMRI GLMs. As reported in the results section, for 2 of the contrasts, there were differences in RT, although not of large magnitude (< 500ms). Due to time constraints, fMRI analyses reported in the thesis do not include RT within the relevant first level GLMs, but these analyses are planned for publication submissions.

fMRI analysis. Three separate general linear models (GLMs) of the functional time series were used to model the time courses of the three phases of the experiment, the training, short probes and long probes phases, using Brain Voyager 20.2 software. For all first level analyses, regressors were convolved with the canonical heamodynamic response function and the time series for each participant was modelled to generate contrasts maps. These contrast maps were entered into second-level group random effects GLMs to test contrasts of interest, in whole brain analyses as well as region of interest (ROI) analyses within hippocampus, caudate and putamen. These regions of interest were predefined, derived from BrainVoyager 20.2 sub-cortical volume of interest resource. For whole brain and ROI analyses, significant clusters of activation were identified following a false discovery rate (FDR) correction of $p < 0.05$, and for whole brain analyses a cluster size threshold of 300 contiguous voxels in transformed Talairach (1 x 1 x 1 mm) space was also applied. Anatomical labelling of above-threshold activation clusters was conducted with the aid of Talariach Client version 2.4.3 (http://talairach.org/client.html). Figures displaying statistical parametric maps are shown superimposed on a single anatomical scan from the participant pool, displayed with permission. All results are reported

following the Organisation for Human Brain Mapping best practice guidelines (Nichols, Das, Eickhoff, Evans, Glatard, Hanke, et al., 2017).

Training phase. For the training phase 9 separate regressors were created consisting of reward periods, first pathways for control, 3-junction routes, 5-junction routes and full routes, and all subsequent pathways for control, 3-junction routes, 5-junction routes and full routes. A pathway consisted of the 2.5 s passive movement period together with the participant's reaction time at the junction at the end of the path, prior to selecting a left or right pathway. The division between first pathways of a route and subsequent paths follows the analysis of Igloi et al. (2010), where first pathways appear to capture route planning processes. Feedback periods (4.5 s) for any incorrect choices, together with the 6 movement parameters, were additionally entered into models as regressors of no interest. A second level, group analysis was conducted based on parameter estimates of regressors derived from these first-level maps, in which the first pathway of control trials was contrasted with the first pathway of the 3-junction route trials. This contrast allowed examination of the brain areas involved in navigating a learned route, and form a useful comparison for other route navigation fMRI investigations (e.g. Igloi et al., 2010).

Short probes phase. For the concatenated 4 runs comprising the short probes phase of the experiment, 15 regressors were created. The regressors comprised reward periods, the first paths of control, sequence or conflict probe trials, and the second, critical, paths of control, sequence and conflict probe trials. Additionally, the first and subsequent paths of 3-junction control trials, 3-junction routes, 5-junction routes and full routes were included in the model. Any feedback periods linked to incorrect responses, together with the 6 movement parameters, were entered as regressors of no interest. A second level, group analysis was conducted based on parameter estimates

of regressors derived from these first-level maps, in which the critical pathway of control probes was contrasted with the critical pathway of sequence probes, where no landmark was present at the critical junction.

For conflict probes, a second level group analysis was conducted with a between subjects single factor ANOVA (sequence responders and landmark responders), on activations on the critical path of conflict probes.

Two separate second level group analyses were planned originally for the contrast between critical control paths and critical conflict probe paths; one for sequence responders and one for landmark responders. Only the direct between-subjects analysis is reported in this thesis. This is because the Brain Voyager software does not calculate FDR thresholds with a sample size of less than 10, and as will be reported in the results section, there were only 8 sequence responders. Therefore, this analysis will have to be performed by alternative means, outwith of the timing constraints of this thesis.

Long probes phase. For the concatenated 4 runs comprising the long probes phase of the experiment, 5 regressors were created. These were the reward periods, first paths of sequence and landmark long probes, and subsequent paths of sequence and landmark probes. Any feedback periods linked to incorrect responses, together with the 6 movement parameters, were entered as regressors of no interest. A second level, group analysis was conducted based on parameter estimates of regressors derived from these first-level maps, in which the first pathway of sequence long probes was contrasted with the first pathway of landmark long probes. In a separate analysis, the subsequent paths of sequence and landmark long probes were contrasted.

Chapter 3: Results

Behavioural Results

Performance.

The mean number of trials required to learn the full route in pre-scanning training was 6.5 (*SD* = 2.89, range 3-13), including the two errorless trials signalling learning to criterion. The mean number of trials containing at least one error made in subsequent full and shorter route trials in pre-scanning training was 1.71 (*SD* = 2.97, range 0-14). In a recognition memory test following behavioural testing, where participants had to correctly sequence screenshots of the individual landmarks of the route, mean correct positioning was 81.49% (*SD* = 25.73%, range 11.1-100%). Thus while performance was generally good, explicit recall of the sequence was relatively poor in a few participants. On the following day, in the 2 warm-up trials before scanning, 21 out of the 24 participants made no errors on these trials, with three participants making one error on the first trial, followed by 2 errorless trials. Thus prior to scanning participants showed good levels of learning of the full route through the VE, and/or the landmark-action associations involved in the route.

For the second phase of the experiment, during the 4 runs which contained short probes, two groups of participants emerged based on their predominant responses during conflict probes. Eight participants made a majority of sequence-based responses (Figure 3, left) and 16 made landmark-based responses (Figure 3, right). An examination of the ratio of sequence to landmark responses within each participant's 24 conflict probe trials revealed that all of the landmark responders showed significant above chance levels of landmark responding, using the binomial test (threshold, $p < 0.05$). Seven out of the 8 sequence responders were also significantly above chance in their proportion of sequence responses. An examination

of the fMRI results reported below excluding the one participant with a majority of sequence-based responses that failed to reach above chance levels, found no difference in the pattern of results. Therefore, this participant was included in the sequence-responder group in the relevant analyses.

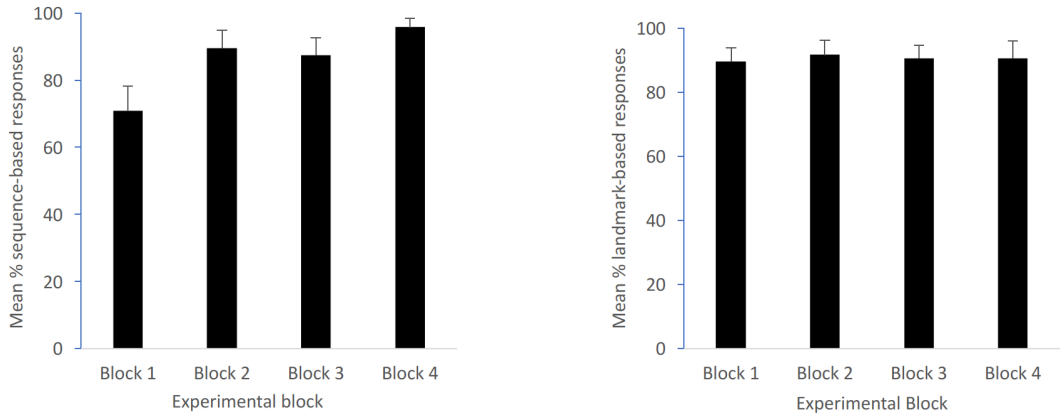

Figure 3. Mean percentages (and *SE*s) for sequence-based responses made within the sequence-responders group (n = 8) and landmark-based responses made within the landmark-responders group (n = 16), for the short conflict probes.

Participants generally showed high levels of performance on short sequence probes, as can be seen from Figure 4 where a correct response was scored if the participant made a sequence-based response. The proportion of correct sequence responses was significantly higher than chance for 23 out of the 24 participants using a binomial test on the number of correct responses out of 24, made by each participant. All participants were included in analyses of the relevant contrasts involving short sequence probes, given that a majority of responses were still correct for the participant that performed relatively poorly. A check was carried out to see whether removing the data of the relatively poorly performing participant affected the relevant fMRI analysis, and this was not the case.

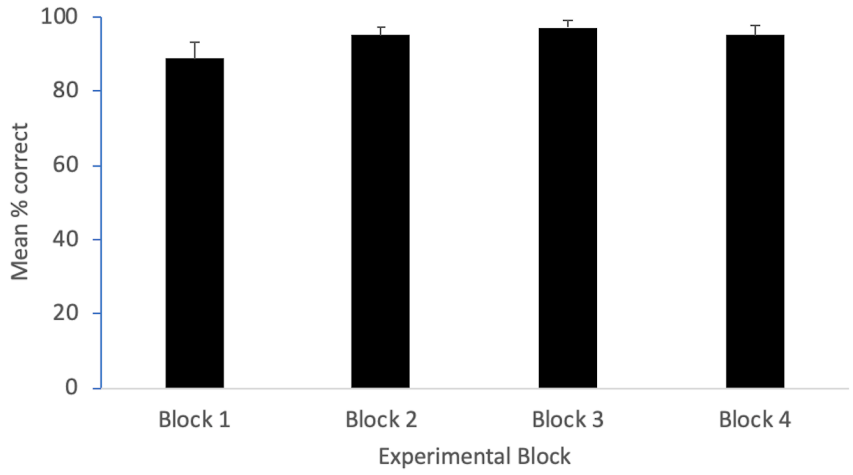

Figure 4. Mean percentages (and *SE*s) for correct, sequence-based responses on short sequence probes ($N = 24$).

In the final phase of the experiment, all participants had a majority of errorless long landmark probe trials. However, 2 out of the 24 participants had a majority of long sequence probes where they made at least 1 error, suggesting relatively poor sequence knowledge. Therefore, these 2 participants were excluded from the analysis of fMRI data (an analysis with all 24 participants was carried out to check results were similar, see "Long landmark and route sequence probes" section below)**.** Figure 5 shows the mean percentage of errorless long probe trials of both types for the remaining 22 participants.

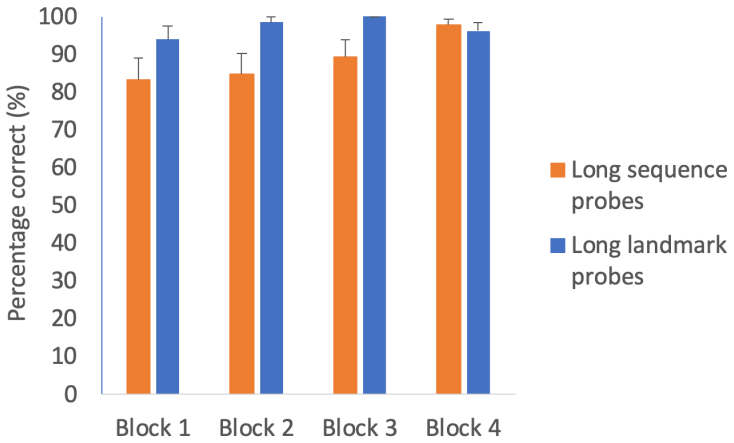

Figure 5. Mean percentages (and *SE*s) of errorless long landmark and long sequence probes (n = 22).

Reaction time.

Comparisons of reaction times (RTs) between conditions used in contrasts of scanning data was conducted to check for any systematic differences between conditions. In terms of training data, the mean RT for the first path of 3-junction training trials was 207.17 ms (*SE* = 33.27 ms), and that for control 3-junction trials was 218.17 ms (*SE* = 29.43 ms), a non-significant difference, with a related samples $t(23) = .94$, $p = .36$.

Figure 6 displays the means and *SE*s for the RTs in short conflict probes for sequence and landmark responders. An ANOVA with block as a repeated measures factor (4 levels) and responder as a between subjects factor (sequence responder, landmark responder), with a Greenhouse-Geisser correction for unequal variances, was conducted on this data. There was a significant main effect for block, F (32.44, 1.47) = 4.27, $\eta^2 = 0.16$, $p = 0.03$, but no significant main effect of responder, F (22, 1) = 1.5, $\eta^2 = 0.06$, $p = 0.23$, or signifiant interaction effect, F (32.43, 1.47) = 1.46, η^2 = 0.06, $p = 0.24$. It is thus unlikely that differences in activations between sequence responders and landmark responders on conflict probes are driven by response times artefacts.

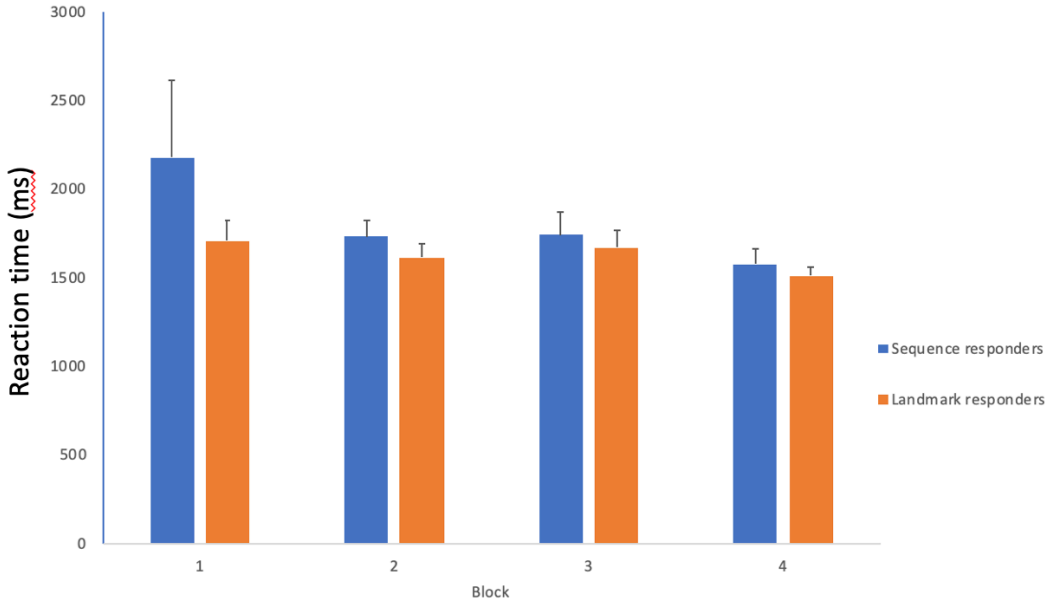

Figure 6. Means (and *SE*s) of reaction times in short conflict probes in the sequence responder and landmark responder groups. *Note*. Individual trials which were not sequence responses in the sequence group, or landmark responses in the landmark group, were not included in the analysis.

Figure 7 displays the means (and *SE*s) of reaction times in the critical path of short sequence probes relative to the equivalent path in short control probes. A repeated measures ANOVA with the factor of block (4 levels) and probe (sequence, control) was conducted applying the Greenhouse-Geisser correction for unequal variances, showing no significant main effect for block, F ((2.29, 47.84) = 2.08, η^2 = 0.08, p = 0.14. There was a significant main effect for probe, F (1, 23) = 22.47, η^2 = 0.49, $p < 0.0001$, and a significant block by probe interaction, F (2.50, 57.41) = 6.78, $\eta^2 = 0.23$, $p = 0.001$. Overall, participants were faster to respond in the control condition, with the largest difference occurring in the first block of short probe trials, with a mean difference of approximately 0.5 s. Thus ideally, RT should be included as a regressor in GLM 1st level modelling for fMRI data contrasts, although due to time

constraints this will be done outwith of the thesis.

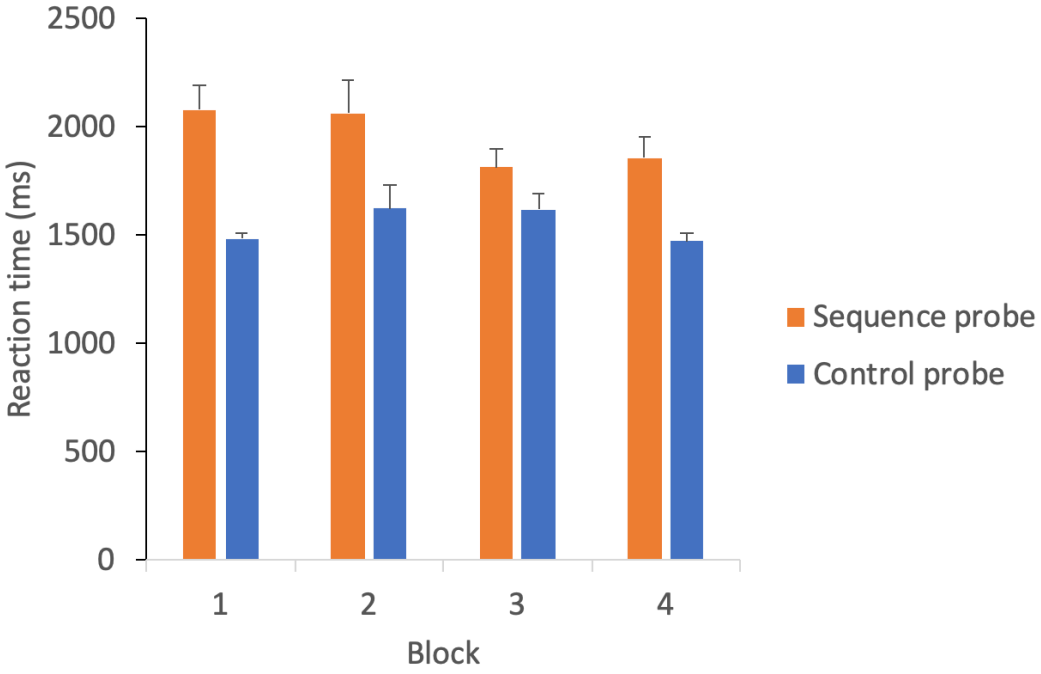

Figure 7. Means (and *SE*s) of reaction times in the critical path of short sequence and control probes, across blocks. *Note*. Individual trials which were incorrect responses in the sequence probes were not included in the analysis.

Finally, for long landmark and sequence probes, reaction times were compared on the first path of each type of trial (Figure 8). A repeated measures ANOVA with block (4) and long probe type (sequence, landmark) as factors was conducted, applying the Greenhouse-Geisser correction for unequal variances. There was a significant main effect of block, $F\ (1.41, 29.69) = 4.15$, $\eta^2 = 0.17$, $p = 0.04$, a significant main effect of probe, $F\ (1, 21) = 8.21$, $\eta^2 = 0.28$, $p = 0.009$, and a significant interaction, $F\ (1.43, 30.02) = 4.93$, $\eta^2 = 0.19$, $p = 0.02$. Inspection of Figure 8 shows that the probe effects were mainly driven by block 1, making it unlikely that an RT confound could account for differences in fMRI activations between conditions. However, planned analyses outwith of this thesis report are planned controlling for RT in GLM modelling of fMRI data.

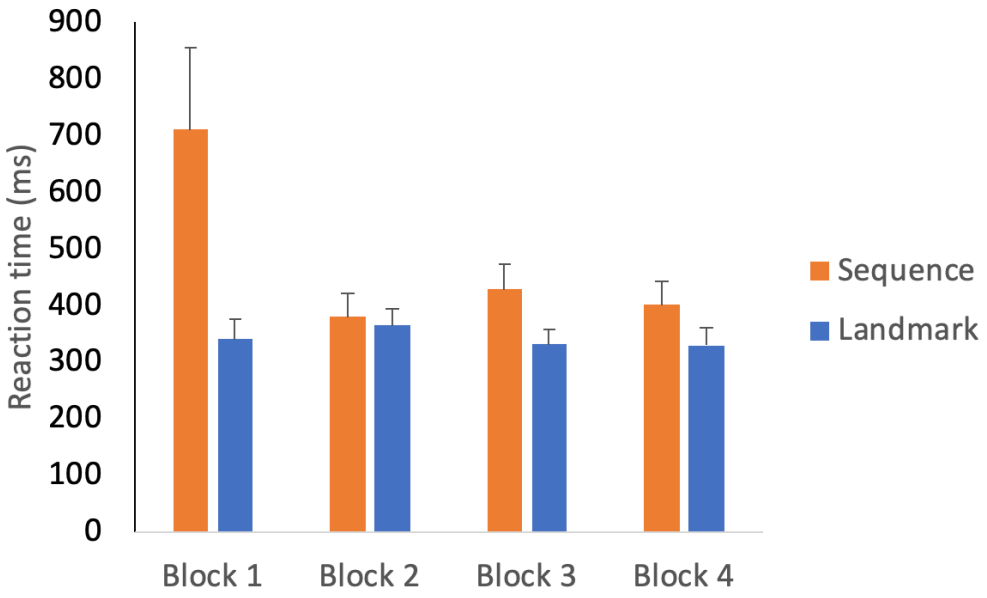

Figure 8. Means (and SEs) of reaction times in the first path of long sequence and long landmark probes, across blocks.

Imaging Results

Training versus control contrasts in the training block.

In order to establish which brain regions were more active during learned route navigation relative to control routes, brain activity during the first path of 3-junction training routes (6 in total for each participant) was contrasted with the first path of the 3-junction control trials (6 in total). Thus activations prior to overt motor behaviour could be contrasted, as in Igloi et al. (2010). Table 1 shows the areas with above threshold activation on the first path of route trials compared to the first path of control trials, in the whole-brain analysis, as well as the reverse contrast. There were no clusters distinguishing route from control trials in the three ROIs, the hippocampus, caudate or putamen.

Table 1

Brain regions more active in the first path of a 3-junction route in contrast to the first path of a 3-junction control trial, in the training block. An FDR correction of $p < 0.05$, and a cluster size threshold of 300 mm^3 was applied.

Area (R/L)	Peak voxel (*x, y, z*)*	*t(23)*	Cluster size ($1mm^3$ voxels)
Route - control			
Inferior/Middle occipital gyrus R	36, -82, -11	7.00	1469
Inferior occipital gyrus L	-36, -88, -8	7.04	1233
Control - route			
Cuneus L	-24, -79, 16	5.64	364

* Talairach coordinates.

Short conflict probes.

In conflict probes a response based on correct sequence in the learned route was pitted directly against a response based on a learned landmark-action association. In order to understand the brain processes underlying these two types of learning, a direct between-subjects analysis was conducted to address whether differing brain regions were engaged when participants made sequence-based versus landmark-based responses on conflict probes. A single factor between-subjects ANOVA was conducted utilizing the beta-maps of each participant's conflict probe condition, both as whole brain and ROI analyses. Under the Khamassi and Humphries (2012) model, it may be predicted that there would be greater hippocampal formation activity, as well as caudate activity, in sequence responders relative to landmark responders, on conflict probes, as a model-based response is required to make a sequence response.

For whole brain analyses, there were several regions that were more active in sequence responders relative to landmark responders (Figure 8 and Table 2), including areas in the parahippocampal cortex and fusiform gyrus associated with spatial scene processing (Cona & Scarpazza, 2019; Epstein & Kanwisher 1998).

There were no activation clusters that were more active in landmark responders relative to sequence responders. There were no above threshold clusters in the hippocampus, caudate or putamen ROIs.

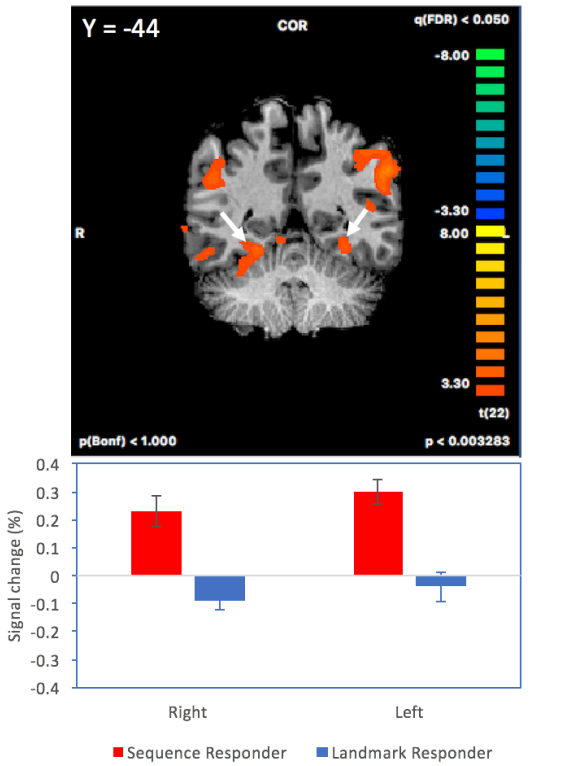

Figure 8. Activation clusters in right and left parahippocampal and fusiform gyrus (white arrows) in sequence-based responders relative to landmark-based responders, in short conflict probes. The mean percentage signal change for each cluster and condition is displayed underneath the corresponding statistical parametric map (df = 22), with error bars representing *SE*s. FDR correction to $p < 0.05$, cluster size threshold 300 mm^3.

Table 2.

Areas more active in sequence responders relative to landmark responders (df = 22), in short conflict probe trials. An FDR correction of p < 0.05, and a cluster size threshold of 300 mm³ was applied.

Area (R/L)	Peak voxel (x, y, z)[1]	t[2]	Cluster size (1mm^3 voxels)
Parahippocampal and fusiform gyrus extending into culmen of cerebellum R	30, -37, -24	5.74	2950
Parahippocampal Gyrus L	-30, -43, -8	4.83	432

Parahippocampal gyrus extending to culmen of cerebellum L	-36, -34, -24	5.28	394
Temporal middle and fusiform gyrus R	48, -43, -11	4.21	500
Inferior temporal gyrus and surrounding cortex R	24, -64, -8	4.81	980
Superior/inferior temporal Gyrus R	39, -64, 22	7.11	8442
Superior temporal gyrus L	-45, -49, 13	4.69	443
Inferior temporal gyrus L	-48, -49, -2	6.66	1900
Middle frontal gyrus (Brodmann 8 & 9) R	45, 11, 34	6.05	5003
Frontal precentral gyrus L	-36, -1, 37	4.51	549
Superior frontal gyrus (Brodmann 9)	24, 50, 37	4.54	799
Middle frontal gyrus (Brodmann 10) R	6, 17, 43	5.74	851
Middle frontal gyrus (Brodmann 10) L	-30, 47, 19	4.53	3787
Inferior frontal gyrus/Insula R	42, 20, -2	8.35	7286
Inferior frontal gyrus/Insula L	-36, 17, 1	8.25	10,008
Insula L	-39, -10, 1	5.40	400
Medial Frontal gyrus R	6, 17, 43	5.74	3516
Cingulate gyrus/posterior cingulate R & L	-6, -25, 28	6.48	3147
Parietal Precuneus L	-12, -67, 41	5.9	1024
Inferior parietal lobule L	-51, -31, 37	5.50	7224
Occipital lingual gyrus L	-18, -70, 1	5.14	1671
Occipital lobe cuneus L	-30, -88, 28	6.46	4192

Cerebellum declive gray R	6, -64, -17	4.57	391
Pons R & L	-12, -28, -26	6.14	1196

Note. One participant in the sequence responder group only contributed 18 trials of each type instead of 24 to the analysis, due to data corruption on one run. [1]Coordinates in Talairach space. [2] *F* values converted to *t* values.

Short sequence probes.

An analysis across all 24 participants was conducted contrasting the critical path of sequence probes with the equivalent control path. Under the Khamassi and Humphries (2012) model, it would be predicted that there would be greater hippocampal formation and caudate activation in the critical path of sequence probes, as prior route trajectory context is necessary to correctly respond in the absence of a landmark. The results of the contrast are displayed in Table 3 and Figure 9. In region of interest analyses, only the hippocampal region showed above threshold activity in the critical path of the control versus short sequence probe, probably due to high levels of default network activity (see right hippocampal formation activation in Table 3). A below threshold cluster of 241 voxels more active in the critical path of sequence probes was found in the left caudate in the region of interest analyses, with no clusters detected in putamen. Given the above threshold caudate clusters found in the whole brain analyses (Table 3), threshold *t*-value FDR cut-offs were inspected for whole brain caudate clusters relative to the predefined caudate ROIs, in order to account for the discrepancy. The *t*-values were slightly lower for the whole brain caudate left and right clusters, thus accounting for the difference between whole brain and caudate ROI analyses results.

Table 3

Whole brain analysis of regions more active in the critical path of the short sequence probe versus the equivalent path of the short control probe, and the reverse contrast. An FDR correction of $p < 0.05$, and a cluster size threshold of 300 mm^3 was applied.

Area (R/L)	Peak voxel (*x, y, z*)*	*t(23)*	Cluster size (1mm^3 voxels)
Sequence - control			
Caudate body R	12, -4, 4	3.93	682
Caudate body L	-6, 5, 10	5.46	410
Middle frontal gyrus R (premotor/SMA)	33, 23, 4	7.15	19411
Middle/Inferior frontal gyrus L (premotor/SMA)	-45, 29, 28	5.46	8991
Precuenus R	6, -64, 41	4.89	4867
Precuneus L	-27, -55, 37	6.00	8438
Medial frontal gyrus R and L (SMA and Brodmann 32)	6, 23, 37	7.45	10815
Posterior cingulate R and L (Brodmann 23)	6, -22, 25	7.78	3105
Middle temporal gyrus R	54, -40, -8	4.22	918
Inferior parietal lobule R	33, -58, 41	7.08	5974
Insula L	-27, 17, 13	5.90	2834
Control - sequence			
Middle and inferior temporal gyrus R	63, -4, -11	4.3	1675
Middle and superior temporal gyrus L	-60, -1, -5	5.9	12227
Superior temporal gyrus L	-48, -55, 22	4.22	827
Occipital cuneus and fusiform gyrus R	39, -79, -5	5.4	3779
Occipital cuneus L	-6, -94, 10	3.97	575
Parahippocampal gyrus extending to cerebellum/declive gray R	30, -49, -11	4.69	2876
Parahippocampal gyrus,	24, -10, -17	5.17	1203

hippocampus and amygdala R			
Fusiform gyrus gyrus extending to cerebellum/declive gray L	-30, -85, -2	5.24	5516
Medial pre-frontal gyrus and surrounding areas R and L	-15, 44, 40	6.51	21346
Parietal postcentral sulcus	63, -25, 16	5.07	3135
Inferior frontal gyrus L	-33, 29, -11	5.08	3186
Inferior frontal gyrus L	-54, 35, 4	3.94	359

* Talairach coordinates.

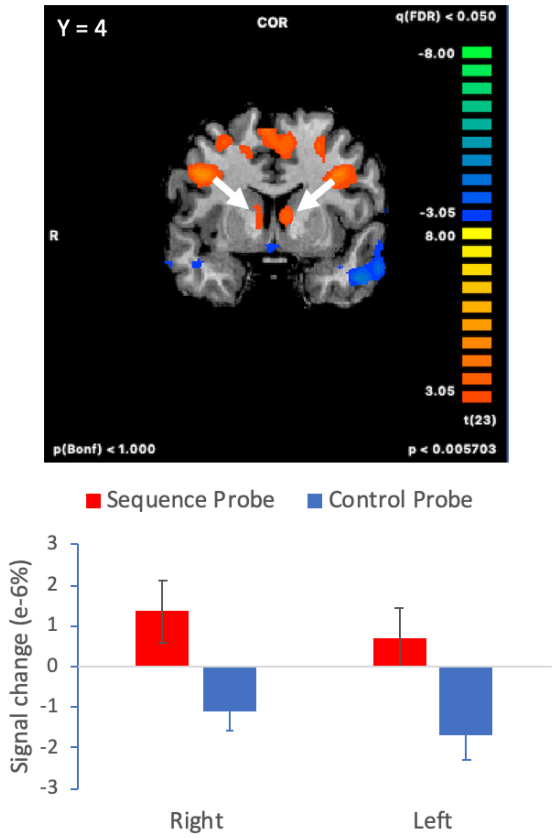

Figure 9. Activation clusters in right and left caudate body (white arrows) in the critical path of sequence probes relative to control probes. The mean percentage signal change for each cluster and condition is displayed underneath the statistical parametric map ($df = 23$), with error bars representing *SE*s. FDR correction to $p < 0.05$, cluster size threshold 300 mm^3.

Thus, the predictions of the Khamassi and Humphries model were only partially confirmed, in that there was greater caudate body activation in sequence probes. No hippocampal or parahippocampal activity clusters were found that were greater in sequence probes, as would be predicted in the Khamassi and Humphries model, with the reverse finding being the case. While the very large activation cluster in medial frontal cortex is indicative of default network activity in the control – sequence probe contrast, it is less clear if the hippocampal formation activity can also be interpreted in this way.

Long landmark and route sequence probes.

In order to acertain which brain regions were differentially active when only route knowledge could be utilised, relative to when only learned landmark-action associations could be utilised, these two types of trials were contrasted across the final 4 runs of the experiment. Two analyses were conducted, one on the first path of each type of trial where a landmark was present in both types of probe. However, in route sequence trials this landmark acted as a starting-point indicator, whereas in landmark trials the first path had no predictive value in terms of which landmarks would follow, as they were ordered randomly. The second analysis was conducted on the subsequent paths, where on landmark trials differing landmarks were present, which were not there on sequence route trials. Two participants were excluded from analyses due to poor behavioural performance on route sequence trials, leaving 22 participants in the analysis. The same analyses including all 24 participants yielded similar results (see Table A1and Figure A1, Appendix 2, for first path analyses including all 24 participants).

First path analysis. Table 4 shows the areas more active in route sequence trials relative to landmark trials. There were no areas that were more active in

landmark trials relative to route sequence trials, an expected outcome given that the visual and motoric demands are identical, with divergence occurring in the movement planning that is required in route sequence trials, relative to landmark trials.

Table 4.

Areas more active in the first path of long sequence probe trials relative to long landmark probe trials in whole brain analyses and region of interest analyses (df = 21). FDR correction to $p < 0.05$, cluster size threshold 300 mm^3.

Area (R/L)	Peak voxel (*x, y, z*)[1]	*t*	Cluster size (1mm^3 voxels)
Whole brain analysis			
Caudate head R, extending into putamen	15, 14, 1	5.30	510
Cuenus R (Brodmann 19 & 18)	24, -88, 22	5.64	735
Cuneus and lingual gyrus R & L, extending into declive gray, R & L	-18, -55, 4	6.79	8437
Regions of interest analyses			
Right caudate (head and body)	15, 14, 1	5.30	2409
Left caudate (head and body)	-9, 5, 7	5.34	1702
Right putamen	18, 14, 1	4.63	770
Left putamen	-21, 11, -2	4.92	1735

[1] Coordinates in Talairach space.

In region of interest analyses, caudate and putamen areas, but not the hippocampus, showed greater activation in the first path of long sequence probes relative to long landmark probes (Table 4 and Figure 10).

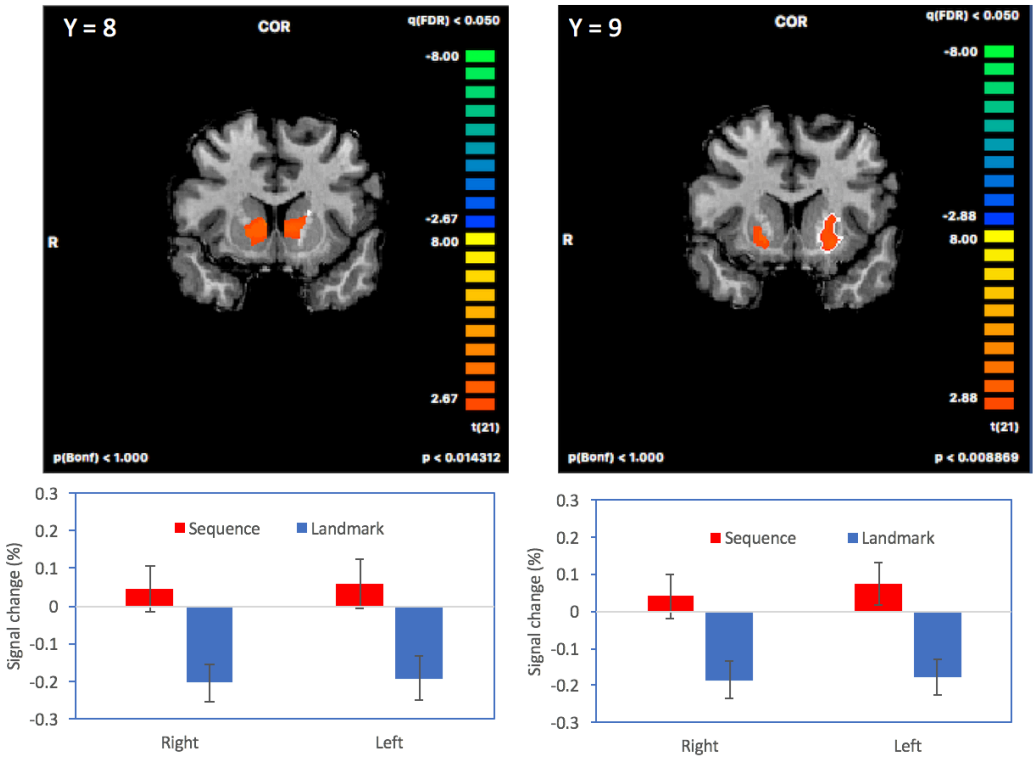

Figure 10. Bilateral activation clusters in caudate (left) and putamen (right) ROIs in the first path of the long sequence probes – long landmark probes contrast. The mean percentage signal change for each cluster and condition is displayed underneath the corresponding statistical parametric map ($df = 21$), with error bars representing SEs. FDR correction to $p < 0.05$, cluster size threshold 300 mm^3.

Subsequent paths analysis. Table 5 shows the areas more active in the 3 pathways following the first junction in long sequence probes (where the memory and monitoring of the left and right sequence of turns was required), relative to the equivalent pathways of long landmark probes. The reverse contrast is also displayed. Region of interest analyses showed higher activations in the three regions of interest, hippocampus, caudate and putamen in the subsequent paths of long landmark probes relative to long sequence probes. Given the very large areas of activation in canonical areas of the default network (Buckner, 2013) in landmark relative to sequence probes (ventromedial prefrontal cortex, anterior cingulate, insula, hippocampal formation, inferior parietal lobule; Table 5), it is unlikely that a task-related interpretation can be

given to the region of interest results in this case. It appears that by this stage of the experiment, landmark-action associations were sufficiently automatic that high levels of default network activity could occur.

Table 5.

Contrasts between long sequence probe trials and long landmark probe trials in whole brain analyses in pathways subsequent to the first junction (df = 21). FDR correction to p < 0.05, cluster size threshold 300 mm³.

Area (R/L)	Peak voxel (*x, y, z*)[1]	*t*	Cluster size (1mm³ voxels)
Whole brain analysis			
Route sequence – Landmark-action			
Cuneus and lingual gyrus R & L	0, -79, -2	7.79	38,951
Ventromedial prefrontal cortex R	24, 56, 4	5.25	6402
Ventromedial prefrontal cortex L	-33, 50, 13	3.47	539
Premotor cortex R	21, -4, 49	5.48	2096
Premotor cortex L[2]	-18, -7, 52	4.03	306
Insula R	27, 23, 7	4.04	1077
Insula L	-27, 26, 4	4.26	585
Middle frontal gyrus (Brodmann 9) R	36, 26, 34	4.04	673
Dorsal anterior cingulate R and L	6, 14, 43	5.56	1369
Landmark-action – route sequence			
Medial pre-frontal cortex/anterior cingulate R	-6, 56, 31	9.01	55,744
Insula/Inferior parietal lobue and surrounding areas R	33, -25, -17	9.30	126,350
Parahippocampal gyrus/Amygdala/Insula and surrounding areas L	-33, -19, -14	9.05	102,587
Primary motor cortex L	-60, -7, 37	4.09	1383

[1] Coordinates in Talairach space. [2] There was an additional cluster of 313 mm³ mainly in white matter adjacent to premotor cortex L.

Chapter 4: Discussion

Results will be summarised and discussed for each of the three different phases of the experiment, the training phase, short probes phase and long probes phase. A brief section on reconciling findings from the two probe phases will follow, prior to a discussion of limitations and future directions for research.

Training

During the training run of the study, the contrast between short route trials and their equivalent controls, in terms of first path activations, can provide insight as to the brain systems utilised for navigating along a familiar route, relative to navigating a route where no decision-making based on route knowledge occurs. Only the left and right middle and inferior occipital gyri, mainly Brodmann 19, showed above threshold activations. This area has been identified in a recent meta-analysis as being an area commonly active in all types of spatial cognition tasks (Cona & Scarpazza, 2019). It is a visual association area recruited in diverse object recognition and spatial working memory tasks. Given that each participant only contributed 6 trials of each type during the training run, the power to detect differences may be low. Despite the dorsolateral striatum (putamen homologue) being repeatedly implicated in spatial tasks involving cue-action associations in lesional studies, no difference in putamen activity was detected in the present study between the route navigation and control condition.

In terms of comparisons with results from earlier studies of the brain systems involved in familiar route navigation, although there are 3 studies in the literature that scanned participants while navigating a learned route, relative to an unlandmarked control where no navigation decisions were required (Brown et al., 2010; Igloi et al., 2010; Marchette et al., 2011), direct comparisons are not possible with 2 of these

studies. Neither Brown et al. (2010) or Marchette et al. (2011) report the contrasts involving their control conditions in landmarkless alleyways. Only Igloi et al. (2010) report details of activation clusters between their familiar route trials and control trials. These authors found activation clusters in hippocampus and caudate, as well as other frontal and medial areas commonly active in spatial tasks (Cona & Scarpazza, 2019).

There are several possible causes of the discrepancy between the results of the present study and those of Igloi et al. (2010). One possibility relates to the different thresholds used in the studies (FDR with $p < 0.05$ in the present study compared to $p < 0.001$, uncorrected, in Igloi et al.). In order to examine this possibility, the training data of the present study was analysed using the same threshold used by Igloi et al. (2010). There were no further clusters identified at this threshold, so it is unlikely that threshold differences could fully account for the discrepancy. A second possibility relates to apparently subtle, but potentially important differences between the control conditions in the two studies. In the present study, passive movement occurred along the VE until the decision point, in all conditions, whereas in Igloi et al. (2010), participants navigated all parts of the route with a joystick. It is possible that the control condition in the present study allowed more default network activity to occur during the passive movement, thus making it less likely that task-related hippocampal activity could be detected, given that the hippocampal formation forms part of the default network (Buckner, 2013). A final possibility is that differences in the environments used in the two studies underlie the differing results. In Igloi et al. (2010), distal landmarks were available in the route navigation condition, allowing allocentric mapping to occur, even if the learned route condition only required a

sequential egocentric spatial strategy. In contrast, in the present study no such distal landmarks were available.

In order to better establish whether navigating a familiar route in an environment that permits mapping using distal landmarks, and one which does not, recruits different brain systems, such conditions would need to be contrasted, directly, with many more trials than those contrasted in the present study.

Short Probes

The short probes phase of the present study was designed as a test of predictions arising from the Khamassi and Humphries (2012) proposal that the division between model-free and model-based responding was a better predictor of hippocampal-dorsomedial striatum (caudate striatum in humans) system recruitment, relative to map-like versus familiar route navigation. Thus participants who followed a sequence response in conflict probes, with out-of-sequence landmarks, and correct sequence responses during sequence probes where landmarks were removed, should recruit hippocampal-caudate systems, as model-based systems are required in these situations. This is either due to a misleading landmark-action association being present in conflict probes, or no landmark being present in sequence probes.

The predictions of the Khamassi and Humphries (2012) model were partially supported, in that there was greater activation in parahippocampal areas (bilaterally) in sequence responders relative to landmark responders on conflict probes. Until connectivity analyses are performed, it is not possible to test the prediction of greater collaboration between caudate and hippocampal formation in order to achieve sequence responses. This greater parahippocamal activity was not found in the contrast between sequence probes and control probes across all participants, possibly due to the large degree of default network activity evinced in control probes. There

was greater caudate activity in sequence probes, as predicted given the greater response difficulty and conflict that would be expected in sequence probes relative to control probes. Again, connectivity analyses may reveal whether this caudate activation shows connectivity with hippocampal formation areas, as would be predicted for model-based performance, under the Khamassi and Humphries (2012) model. This greater caudate activity in sequence probes is also consistent with the findings of Igloi et al. (2010) in their contrast between sequential egocentric probe trials and control trials.

In terms of other regions of activation arising from whole brain analyses in both the between-subjects contrasts, and the within-subjects contrasts in sequence probes versus control, several overlapping areas were identified. One of these was the supplementary motor area (SMA), bilaterally. The SMA was also found to be more active in sequential egocentric probe trials (relative to control trials) in the study of Igloi et al. (2010). The SMA appears to be involved in all types of task involving sequencing of elements, be these spatial, motor, linguistic or musical (review in Cona & Semenza, 2017), with some debate as to the functional role of the SMA in brain systems underlying different tasks requiring sequencing.

The middle temporal areas (particularly fusiform gyrus), the inferior parietal lobule and insula, bilaterally, were also active in sequence responders and sequence probes in the present study, similar to Igloi et al. (2010). These areas are all commonly activated in a variety of spatial tasks (Cona & Scarpazza, 2019), and may be involved in working memory and attentional aspects of spatial task performance. The insula may play a role in prioritising stimuli depending on task demands, particularly in tasks where a "retrocue" signals which stimuli held in working memory are required for task response (Myers, Stokes & Nobre, 2017). The sequence

probe, as well as a sequence response to a conflict probe, can be thought of as a retrocue task, in that the absence or mis-placement of the landmark at the junction on the critical path of the probe trial serves to cue the participant that the memory for the previous path will be required.

In summary, there was partial support for the role of the hippocampal formation being recruited in model-based decision making relative to model-free, landmark-action, responses while navigating a familiar route. In the present study, it was the parahippocampal area, rather than the hippocampus itself, that showed greater activation when sequence responses were required, consistent with the recent meta-analysis by Cona and Scarpazza (2019), indicating more reliable activation of parahippocamal areas relative to the hippocampus itself across a variety of spatial tasks. Whether collaboration between hippocampal formation and caudate occurred as predicted (Brown et al., 2010; Khamassi & Humphries, 2012), requires connectivity analyses to be performed.

Long Probes

Two differing predictions were made concerning the contrast of the first path of long sequence probes versus long landmark probes. The first was that both putamen and caudate may be implicated in sequence planning, and therefore greater activation in these areas may occur relative to the landmark probe where planning is not possible. Such a result is consistent with the lesional study of Pistell et al. (2009), where the effects of dorsolateral and dorsomedial lesions on sequential egocentric maze performance were more severe than those typically reported for hippocampal lesions (Bresnahan et al., 1988). Greater putamen activation would also be consistent with the proposals of Dezfouli and Ballaine (2012; see also Smith & Graybiel, 2016), where it is increased behavioural chunking as a result of learning that underlies the

role of putamen in habitual behaviour, as opposed to being a neural substrate for model-free learning. Alternatively, more activation of the hippocampal formation-caudate system may be predicted (Brown et al., 2010; Khamassi & Humphries, 2012) due to the need to base upcoming choices in the sequence probes on the landmark presented at the start of the probe, requiring use of model-based learning.

The results from the contrast between the first path of long sequence probes and long landmark probes provided support for the theories linking the putamen to initiation of learned sequential behaviour (Dezfouli and Ballaine, 2012; Graybiel & Smith, 2016). The greater bilateral putamen activation was only found in the ROI analyses, whereas caudate activation was above threshold in both the whole brain and ROI analyses. These results are consistent with those of Igloi et al. (2010), examining the first path of their sequential egocentric trials, where whole brain analyses did uncover some caudate activation, but no putamen activation (ROI analyses were not conducted in this study within the striatum). Conversely, no hippocampal or hippocampal formation increases in activation were uncovered for the long sequence probes, in the present research, thus going against predictions based on the Khamassi & Humphries model. These results also appear in conflict to the findings of Igloi et al. (2010) in terms of greater hippocampal activity in the first path of sequential egocentric probes. It is possible that the more open environment, with distal landmarks, available in the Igloi et al. study was critical to the greater hippocampal activation found in that study, as opposed to the trajectory planning process itself. Of course this interpretation would not preclude a role for the hippocampus in this form of navigation (Rondi-Reig et al., 2006), but this role may not necessarily manifest in greater activation within the context of fMRI (Cona & Scarpazza, 2019).

Few navigation studies report putamen activation, in contrast to the considerable lesional literature implicating the dorsolateral striatum in cue-guided responding, a point emphasised by Patterson and Knowlton (2018), in their recent review of the fMRI literature in relation to putamen function. The few studies that do report putamen activation, (Iaria et al., 2003; Wegman et al., 2014; Woolley et al., 2013) have in common the ability of participants to plan a trajectory to a goal, versus conditions in which this planning is not necessary, or not possible. In the study by Iaria and colleagues (Iaria et al., 2003), a win-stay task was utilised where participants memorised a set of arms to visit in a radial maze, versus a control condition picking up visible objects from the end of maze arms. In Woolley et al. (2013), participants conducted a well learned VE version of a Morris water maze, where only four possible starting points were utilised, in contrast to "purposeless wandering" in a control condition. Thus some planning could occur of trajectories from well-learned starting points. The results of the present study in terms of putamen activation in the long sequence probes appear to fit within this set of findings linking putamen activity to familiar trajectory planning. An interesting, exploratory question with regard to connectivity analyses would be the relation (positive, negative or uncorrelated) that exists between putamen and caudate activation within the sequence probes, and any relation to these to connectivity with other brain areas.

Other areas that were more active during the first path of long sequence probes relative to long landmark probes were the cuneus and lingual gyri, bilaterally. These areas are associated with visual memory and imagery, and are commonly activated across a range of spatial tasks (Cona & Scarpazza, 2019; Nemmi, Boccia, Piccardi, Galati & Guariglia, 2013).

In terms of the contrast between long sequence probes and long landmark probes in paths following the first path, findings are hard to interpret, given the large clusters of activity found in default network areas in landmark trials relative to sequence trials. At this stage of the study, it appears that the individual landmark-action associations were so automatic that there were insufficient task demands to suppress default network activity.

Reconciling findings from short probe and long probe phases

The findings from the present study provide support both for the view that hippocampal formation-dependent processes are involved in egocentric sequential aspects of learned route navigation (the results from the short probes phases), and also that egocentric sequential route navigation is subserved by striatal systems (results from the long probe phases). It can be argued that these findings are not in conflict with each other, when key differences between short and long probes are considered. In short conflict or sequence probes, an unpredictable retrocue (the out of sequence landmark, or the absence of a landmark respectively) requires a model-based response, drawing on memory for the preceding landmark. In the long sequence probe, the initial landmark acts as a reliable cue to a well-learned egocentric sequential trajectory, and the putamen is critical to the concatenating of action chunks into larger, automatic action sequences, according to the framework of Dezfouli and Balleine (2012; also Pennartz et al., 2011 and Smith & Graybiel, 2016).

The critical question, both for correlational studies such as fMRI and more invasive techniques, is whether during learning of egocentric sequential routes, model-based systems are necessary, with a gradual transfer of control to dorsolateral striatum/putamen occurring as the sequence becomes more automatic or habitual. Such studies tracking the learning process have yet to be done, both in lesional

studies, and in human imaging studies. The original work on egocentric sequential navigation by Rondi-Reig and colleagues (Rondi-Reig et al., 2006) utilised mice with genetically-mediated hippocampal disfunction. Thus the question of whether hippocampal lesions following egocentric sequential learning in a star maze in intact rodents would still impair performance, remains unanswered. The study by Pistell et al. (2009) demonstrates that acquisition of egocentric sequential maze navigation is severely affected by striatal lesions, but again, it is not known whether such lesions would also impair performance subsequent to acquisition in intact animals. Following Dezfouli and Ballaine (2012, also Smith & Graybiel, 2016), it may be predicted that hippocampal lesions would have less effect following well learned egocentric sequential route navigation, whereas striatal lesions, particularly in dorsolateral striatum, should impair performance even after learning. In terms of human neuroimaging, studies that can track the learning process in egocentric sequential route navigation could test predictions about the brain systems underlying any transfer of control to putamen with learning.

Limitations and future directions

The present research followed the suggestions of Khamassi and Humphries (2012) to reconsider the spatial navigation literature within a parallel spatial memory systems framework, whereby the main division between whether tasks draw on hippocampal or (dorsolateral) striatal systems is whether they can be considered model-free or model-based tasks. This division cuts across the more traditional divide between map-based or cue-based navigation tasks (O'Keefe & Nadel, 1978), where following a prescribed route was a classic example of a cue-based task. Our results indicated a role for the hippocampal formation in route-following when decision-making required an accurate knowledge current position along the route trajectory as

a whole, unsupported by landmark cues that would normally be expected. Our results also indicated a role for putamen and caudate in sequence planning, particularly when such planning is necessary for successful route navigation, as in the long sequence probes of the present study.

Various factors limit somewhat the conclusions that can be drawn from the present study and should be considered in future research. One of the limitations concerned the type of control trial used, whereby participants navigated through an un-landmarked route where choices were forced at junctions through the use of barriers. Although modelled on the earlier study of Igloi et al. (2010), these control conditions were found to generate a large degree of default network activity, which may have interfered with any genuine task-related effects in areas such as the hippocampal formation. A slightly more demanding control condition, for example where a consistent colour cue determines whether a left or right turn is required, may have been more appropriate.

A second limitation of the short conflict probes was the imbalance, and therefore the low power, in the groups spontaneously selecting to make a sequence- versus landmark-based response. Perhaps a design in which blocks were presented whereby instructions biased participants to make either a sequence-based response or a landmark-based response, would have yielded data sets with greater power.

Future studies could pursue the questions raised by the present research, as well as the lesional results of Pistell et al. (2009), by studying the brain correlates, via fMRI, of pure egocentric sequential learning, using un-landmarked routes. Further, tracking of changes as a result of learning, and over-learning, of the route could be the focus of the research. Such studies present challenges, not least how to overcome the issue of participants attempting to learn a verbal list of directional turns at choice

points. However, such studies could help reveal the systems underlying egocentric sequential navigation, currently an understudied area in the field.

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Appendix A

Participant instructions for all phases of the experiment

Behavioural training (day before scanning)

In this study we are assessing human navigation using a computer generated virtual environment, which you will view from a first person perspective. You will be placed into a garden hedge-maze, and your task is to learn the way to the garden house within the maze. In the garden maze you will be stopped at each junction, at which point the appearance of arrows at the junction is a signal for you to decide whether to turn left or right. There are landmarks at each junction to help you learn which direction to choose, and to indicate your choice you should press the left or right arrows on the keyboard.

During training you will receive feedback about your choice at each junction. When you make an incorrect choice, the screen will fade red, and you will be placed back at the **same junction**. When you make a correct choice, you will move down the correct path and stop at the next junction.

Importantly, the way to the garden house is the same throughout the experiment. At the beginning of the experiment, we'll keep repeating the same trial until you have managed to complete two successive trials without making any errors. After you've learned the route, some trials may be shorter than others, and you might not begin at the start of the route. Remember, though, the route to the garden house is always the same.[1]

Scanning training (1st block)

In this part of the experiment you will receive more training trials as before, to make sure you have not forgotten the route. In addition, you there will also be trials where some paths are blocked off by a fence. On these trials, you will have to choose the unblocked paths at each junction.

Scanning short probes (blocks 2-3 and 5-6, with block 4 serving as the structural scan)

In this part of the experiment you will again have to walk the route to the garden house. On most trials you will receive feedback about your decisions in the same way as before.

However, there will be some trials where something might have changed, and in which no feedback is given. On these trials, as soon as you have chosen to turn left or right the trial will end without telling you whether you made the correct decision or not. Try to make the correct response based on knowing you are on the same route that you have learned.

Scanning long probes (blocks 7-10)

In this stage of the experiment you will receive two different trial types.

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[1] Just prior to scanning, participants carried out "refresher" routes through the full route, simply with a verbal instruction that they would be reminded of the full route until they had 2 errorless trials. Twenty one out of the 24 participants made no errors and thus reached the criterion of 2 errorless routes in the minimum number of 2 trials. The maximum number of refresher trials given was 3.

In route trials you will see one landmark at the beginning of each trial, which you can use to tell where along the route you are. However, the other landmarks have all been removed from the environment. The route hasn't changed though, so you can make correct choices at each junction based on what you have learned.

In landmark trials we have changed the order of the landmarks from what you have learned. To make the correct decision at each junction, you need to base your decision on the direction you would have turned when you saw that landmark during the normal route to the garden house.

Before each trial begins, you will be told whether it is a route trial or a landmark trial.

Appendix 2

Analyses of the first path of long sequence versus landmark probes including all 24 participants

Table A1.

Areas more active in the first path of long sequence probe trials relative to long landmark probe trials in whole brain analyses including all 24 participants (df = 23). FDR correction to p < 0.05, cluster size threshold 300 mm³.

Area (R/L)	Peak voxel (*x, y, z*)[1]	*t*	Cluster size (1mm³ voxels)
Caudate head and body R	12, 11, 4	4.70	590
Cuenus R (Brodmann 19 & 18)	24, -88, 22	4.30	501
Cuneus and lingual gyrus R & L, extending into surrounding cortex and declive gray, R & L	-18, -55, 4	7.05	15005
Precuneus R	15, -70, 38	4.62	439
Cingulate gyrus extending to middle frontal gyrus R (Brodmann 24)	9, 8, 46	4.95	300
Cingulate gyrus L	-12, 8, 40	5.25	662
Putamen L	-9, 5, 7	5.74	878
Cerebellumm Culmen L	-9, -40, -8	5.07	716

[1] Coordinates in Talairach space.

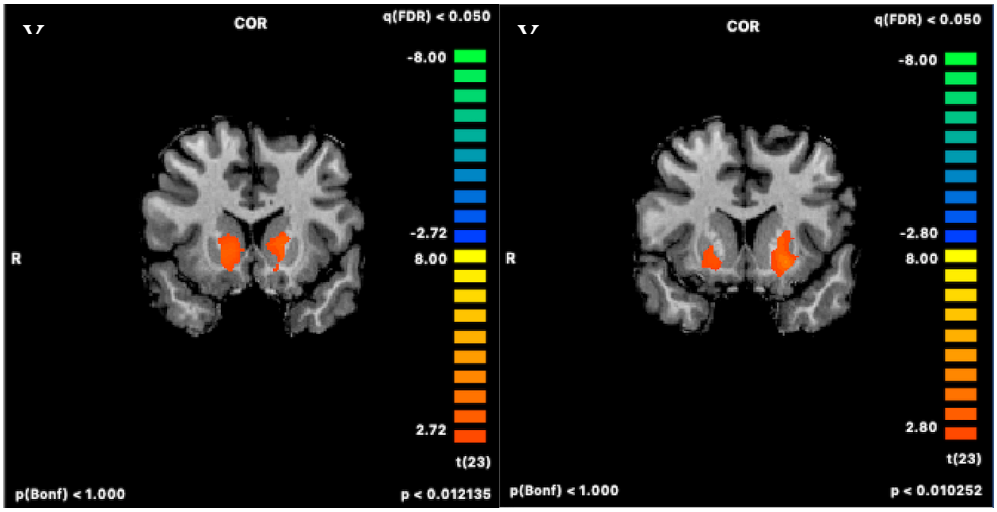

Figure A1. Bilateral activation clusters in caudate (left) and putamen (right) in the first path of the long sequence probes – long landmark probes contrast, including all 24 participants, in ROI analyses. FDR correction to $p < 0.05$, cluster size threshold 300 mm^3.