Into the future with little past: Exploring mental time travel in a patient with damage to the mammillary bodies/fornix

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Into the future with little past

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Into the future with little past

Abstract

Objective: Remembering the past and imaging the future are both manifestations of "mental time travel" (Tulving, 1985). These processes have been found to be impaired in patients with bilateral hippocampal lesions. Here we examined the question of whether future thinking is affected by other Papez circuit lesions, namely damage to the mammillary bodies/fornix.

Method: Case (SL) was a 43 year old woman who developed dense anterograde and retrograde amnesia suddenly, as a result of Wernicke-Korsakoff's syndrome. A region of interest volumetric MRI analysis was performed. We assessed past and future thinking in SL and 11 control subjects of similar age and education with the adapted Autobiographical Interview (AI). Participants also completed a battery of neuropsychological tests.

Results: Volumetric MRI analyses revealed severely reduced fornix and mammillary body volumes, but intact hippocampi. SL showed substantial, albeit temporally graded retrograde memory deficits on the adapted AI. Strikingly, whilst SL could not provide *any* specific details of events from the past two weeks or past two years and had impaired recall of events from her late 30s, her descriptions of potential future events were normal in number of event details and plausibility.

Conclusions: This dissociation of past and future events performance after mammillary body and fornix damage is at odds with the findings of the majority of patients with adult-onset hippocampal amnesia. It suggests that these non-hippocampal regions of the Papez circuit are only critical for past event retrieval and not for the generation of possible future events.

Into the future with little past

Into the future with little past

Introduction

Tulving (2002) described episodic memory as the ability to conjure personally experienced events of a known temporality that are rich in contextual details. Recently, this skill has been linked to the ability to mentally pre-experience possible personal future events, termed episodic future thinking (Atance & O'Neill, 2001), at the behavioural and neurological level (for a recent review see Addis & Schacter, 2012) .

In healthy participants, studies have demonstrated similarities in the phenomenological detail of personal past and future event descriptions (Addis & Schacter, 2008; D'Argembeau & Van der Linden, 2004; Hassabis, Kumaran, Vann, & Maguire, 2007; Levine et al., 1998; Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002; Stuss, 1991). For example, as temporal distance to the present increases, the amount of episodic details (Addis & Schacter, 2008), and vividness (D'Argembeau & Van der Linden, 2004) drops in both past and future event descriptions. The behavioural similarities between past and future events have been further corroborated by findings of shared neural correlates across the two processes in functional imaging experiments (Buckner & Carroll, 2007; Okuda et al., 2003; Szpunar, Watson, & McDermott, 2007). Neuroimaging studies involving both tasks reveal activations of a core brain network, involving the medial and lateral temporal lobe, lateral parietal, medial prefrontal and posterior cingulate/retrosplenial regions (Schacter & Addis, 2007; Schacter, Addis, & Buckner, 2007).

Studies involving patients with adult onset medial temporal lesions have provided evidence of the hippocampus' importance in past and future thinking. Of the 22 patients reported in the literature with adult-onset anterograde and retrograde

Into the future with little past

amnesia caused by bilateral medial temporal lesions, 15 have shown significant

problems describing both past events and possible future ones: (MC in Andelman,

Hoofien, Goldberg, Aizenstein & Neufeld, 2010; 4 out of 5 cases in Hassabis et al.,

2007; DB in Klein, Loftus & Kihlstrom, 2002; 8 patients in Race, Keane & Verfaelli,

2011; NN later named KC in Tulving, 1985 and Rosenbaum et al., 2005), but seven

have not (1 out of 5 cases (PO1) in Hassabis et al., 2007; 6 cases, albeit with intact

recall of remote events, in Squire et al., 2010). The Adapted Autobiographical

Inventory (Addis & Schacter, 2008) was created to explore past and future thinking

using the same technique and matching time intervals in both temporal directions.

This has been used, for example, to examine changes in past and future thinking in

older versus younger subjects.

Based on this behavioural and neuroanatomical evidence, Schacter and Addis

(2007) proposed the *constructive episodic simulation hypothesis*; episodic future

thinking is achieved through the flexible recombination and integration of (past)

episodic memory traces into novel events via relational processes. According to

Schacter and Addis (2007), conjuring potential new experiences draws upon various

features of encoded experiences, including outputs from perceptual systems and

interpretation by semantic systems, in addition to the episodic memory network.

Hence activation of a large-scale brain system, which depends heavily on the

hippocampus for relational processes used during the recombining process (Schacter

& Addis, 2007; Schacter, Addis, & Buckner, 2007), seems to be crucial for both the

ability to retrieve personally experienced past events and episodic future thinking.

It should be noted that the hippocampus is only the first relay station of the

episodic memory or Papez circuit, which encompasses the hippocampus, fornix,

mammillary bodies, thalamus and anterior cingulate (see Carlesimo, Lombardi &

Caltagirone, 2011 for a review). Studies in both humans and animals have found that damage to any of the relay structures involved in this circuit results in episodic memory retrieval deficits (for a review see Aggleton & Brown, 1999). Given the association between deficient past and future thinking found in patients with damage in other parts of the circuit (namely the hippocampus; Andelman et al., 2010; Hassabis et al., 2007; Klein et al., 2002; Race et al., 2011; Rosenbaum et al., 2005; Tulving, 1985), we sought to determine whether the same pattern would be observed when the hippocampus is intact but other Papez structures are damaged.

Patients with Wernicke-Korsakoff's syndrome (WKS) provide an ideal human lesion model to test this notion, as neuropathological studies have consistently found atrophy in the mammillary bodies (Sheedy, Lara, Garrick, & Harper, 1999) and occasionally in the anterior thalamic nuclei (Harding, Halliday, Caine, & Kril, 2000). Atrophy in these brain regions is associated with an amnestic presentation (Jung, Chanraud, & Sullivan, 2012) and/or selective deficits in contextual memory retrieval (Tsivilis et al., 2008; Vann, 2010; Vann et al., 2009). Patients with WKS also show severe deficits in the recall of past events (i.e., autobiographical memory), with most patients having better recall of remote memories than recent ones (Kopelman, 1989; Kopelman, Stanhope, & Kingsley, 1999). Some patients with WKS confabulate (produce false statements) about both the past and the future (i.e., La Corte, Serra, Attali, Boisse & Dalla Barba, 2010), typically spontaneously (Schnider, 2008). In two published cases, confabulation related only to future events (Burgess & McNeil, 1999; Schnider et al., 2013). In both cases, confabulations were recurrent, spontaneous and fixed: concerned an obligation to which they felt a need to respond. The obligation was related to a specific episode from the past, but was not relevant for the future. To our knowledge, no study to date has investigated whether ability to

construct relevant future events on demand is also impaired in WKS patients with selective mammillary body damage who present with anterograde and temporally limited retrograde amnesia.

The current study aims to fill this gap by investigating the diencephalic contribution to episodic future thinking in a case with WKS amnesia (SL). Importantly, SL showed selective damage to the mammillary bodies and fornix, while the anterior thalamus and hippocampus remained relatively intact. Furthermore, we employed a structured, detailed approach to contrast past and future thinking: the adapted Autobiographical Interview (Addis & Schacter, 2008). Given the behavioural similarities between past and future thinking found in healthy participants and in patients with bilateral mesial temporal lesions we predicted that SL would show impaired future thinking due to her striking deficits in episodic memory.

Method

Approvals were granted by the Royal Prince Alfred Hospital, University of Sydney (Protocol No X09-0338 & HREC/09/RPAH/564) and University of New South Wales (Biomedical, ref. #10035) Human Research Ethics Committees. All participants provided informed consent.

2.1 Case Description

SL was a 43-year-old, right-handed woman who presented in February 2009 with a 10-day history of increasing ataxic gait, blurred vision, confusion and amnesia. She was diagnosed with Wernicke Korsakoff's encephalopathy caused by nutritional deficiency and high alcohol consumption (2 litres of wine per day for 7 years). Treatment was intravenous thiamine and withdrawal of alcohol. Her initial MRI as well as a later one, from December 2009 confirmed diffuse cerebral and cerebellar

atrophy as well as hyperintensities bilaterally in the mamillary bodies and periaqueductal grey. In the 2009 MRI, atrophy is visible in this region (Figure 1). A region of interest volumetric analysis was conducted on SL's fornix, mammillary bodies, thalami and hippocampi, and compared to a control group (*n*= 15) of similar mean age (*M*=48.3; *SD*=8.4). All volumetric analyses were conducted using the VBM and FIRST toolboxes in FSL (http://www.fmrib.ox.ac.uk/fsl/). The regions of interest (ROI) boundaries were established by masking the whole brain with the respective regions from the Harvard-Oxford probabilistic atlas and the Juelich Histological atlas. There is currently no anatomical ROI for the anterior thalamus for T1 scans, as the borders cannot be delineated on a macroscopic level. Instead, we used the first third of the anterior thalamus as a proxy regional measure, which we have also used in previous studies (Hornberger et al. 2011; Tan et al., 2013; Tu et al. 2015). All ROIs were corrected for total intracranial volume (TIV) to account for brain size differences across participants. SL had reduced mammillary body volumes (mm^3) [SL =126; controls: mean = 235 (SD = 30.3)] and fornix volumes (mm^3) [SL = 910; controls: mean = 1201 (SD = 123.4)], but relatively intact anterior thalamus (mm^3) [SL = 3460; controls: mean = 2955 (SD = 585.3)] and hippocampal volumes (mm^3) [SL = 7115; controls: mean = 7579 (SD = 424.1)] (Figure 2). Statistical analyses of the region-of-interest (ROI) volumes, employing single case statistics developed by J. R. Crawford and Garthwaite (2007), revealed significant volume changes for the mammillary bodies ($p < 0.01$) and fornix ($p < 0.025$) but not for the anterior thalamus ($p > 0.1$) and hippocampus ($p > 0.1$).

----- Figure 1 & Figure 2-----

From the time of her admission, SL's clinical presentation was notable for her dense anterograde and retrograde amnesia. For example, during her initial illness, she

had no recollection of her current partner of several years, but instead thought that she was still living in London with her ex-husband. According to the history provided by a relative, this would have been her situation 16 years earlier. In addition, she showed no day-to-day memory for events. On follow up conducted a year after the initial admission she was sober. She came to realise who her current partner was. She had not returned to work, but had a volunteer role in a charity shop which she attended a few times per week. Each time she went there as for the first time. One problem that arose as a result of her ongoing poor memory was a great accumulation in second hand clothes that she brought home because she had forgotten her previous purchases.

SL had completed a Bachelor's degree in Economics (15 years of education) and had worked in the related field for some years after graduating. She had not worked, however, for several years prior to admission. She had no other known pre-existing history of psychiatric or neurological disorders. When she was tested, she was taking oral Thiamine and was no longer drinking alcohol. A mood inventory (Depression, Anxiety Stress Scales; Lovibond & Lovibond, 1995) indicated no symptoms of stress, anxiety or depression.

Results from SL's standard neuropsychological assessment (all carried out $\geq$ 9 months post onset) are shown in Table 1. Relative to normative data, SL demonstrated severely impaired anterograde memory on tests involving verbal (Verbal Paired Associates from the Wechsler Memory Scale – Third Edition, Wechsler, 1997b; Rey Auditory Verbal Learning Test, Lesak, 1976) or visual (Rey Complex Figure Test; Rey, 1941) material: delayed recall $\leq$ 5$^{\text{th}}$ percentile in all instances. In addition, SL's generativity/verbal fluency was also severely impaired, scoring in the bottom 1$^{\text{st}}$ percentile for the Controlled Oral Word Association Test (Benton & Hamsher, 1976). Nevertheless, she scored within the age-appropriate range for all other measures of

Into the future with little past

executive functioning tested: working memory (Digit Span Backward from the Wechsler Adult Intelligence Scale –Third Edition; Wechsler, 1997a), mental flexibility (Trail Making Test - B; Partington & Leiter, 1949), response initiation and suppression (Hayling Test; Burgess & Shallice, 1997) and visuospatial reasoning (BrixtonTest; Burgess & Shallice, 1997). The test of past and future thinking (as described in the next section) was administered in July 2010.

----- Table 1 -----

Materials

First, a procedure used by Addis et al. (2008) was employed to investigate recall of past and construction of future autobiographical events. Narratives were scored using a scoring procedure for the Autobiographical Interview developed by Levine and colleagues (2002). Participants were asked to recall or imagine in as much detail as possible four specific events from each of the following time periods: past two years (excluding last month), past two weeks, next two weeks and next two years (excluding next month), each within a three-minute time limit, including general probing. Immediately after completion of each event description, participants dated and rated it for phenomenological detail on (i) vividness (1= vague to 6= extremely clear/as if it is happening now), (ii) how the event affected them emotionally (1= no change in how I felt to 6= tremendous emotional change) and (iii) how personally significant the event was to them (1=no importance at all to 6= of great importance).

The order of Direction (past, future) was counterbalanced across control participants. While five participants recalled the past first, six participants recalled the future first. However, in both temporal directions (past or future) participants were asked to recall proximal (two weeks) before distal (two years) events to reduce

cognitive load. SL was asked to recall past events first and future events second.

Mann Whitney U test showed that the order or recall did not affect neither the number

of internal (past weeks, $p=.33$, past years, $p=.66$; future weeks, $p=.54$, future years,

$p=.23$) and external (past weeks, $p=.43$, past years, $p=.43$; future weeks, $p=.18$, future

years, $p=.43$) details generated nor the phenomenological ratings: vividness (past

weeks, $p=1.00$, past years, $p=.33$; future weeks, $p=.93$, future years, $p=.54$), emotional

impact (past weeks, $p=.93$, past years, $p=.79$; future weeks, $p=.54$, future years

$p=.06$) and personal significance (past weeks, $p=.08$, past years, $p=.25$; future weeks,

$p=.25$; future years, p=.25)

Second, the original Autobiographical Interview (AI, Levine et al., 2002) was

used to examine the temporal extent of SL's autobiographical memory deficits.

Participants were asked to recall one specific event from each of four life periods:

Teenage Years (11-17 years), Early Adulthood (18-35), Middle Adulthood (36-one

year prior to assessment) and Recent Time (last year). On completion of free recall of

each event a general probe was given.

Both interviews were audio taped, transcribed verbatim and scored using the

AI manual. The AI separates details that are central to the episode (internal/episodic)

from details that are episode non-specific (external/semantic). In addition, it

distinguishes types of internal (event, time, place, perceptual, and emotion/thought)

and external [semantic, repetitions and other (such as metacognitions or

editorilizations)] details. Total recall scores (free recall + recall after general probe) of

internal and external as well as different types of details were obtained for each period

in the adapted and original Autobiographical Interviews. All transcripts of the first

interview were scored by the main investigator (JT) who was trained in scoring. Ten

randomly selected past and future narratives were scored by another independent,

12

trained researcher. The intraclass correlations were high for internal (*ICC* =.89, *p* <.01) and external (*ICC* =.83, *p*<.01) details. The transcripts of the second interview were first segmented into informational bits or details, classified as a unique occurrence, observation or thought, typically expressed as a grammatical clause. Each detail was then categorised as ''internal'' or''external'', representing episodic and semantic memory, respectively. Here, we focused on the retrieval of internal (i.e., episodic) details as an index of overall autobiographical event recollection. Internal details were those details relating directly to the main episode, located within a specific spatiotemporal context, and reflected episodic re-experiencing. All scoring was performed by a trained scorer (MH) who was trained on an independent set of stories with high rating consistency (ICC = .91, p < .01). ……Michael/Sicong????...

Finally, phenomenological qualities of events recalled in the first interview were also rated by two independent raters blind to the group membership (SL vs Controls) when a significant difference was found between SL's and control participants' ratings of events phenomenological qualities. To further quantify the scene construction ability, which was not rated by study participants but is of theoretical significance, all transcripts of events from the first interview were also rated for contiguity (1= the event was a collection of separate images to 6= I could see the event unfolding in front of my eyes) by the same two independent raters. The mean ratings were used in the analyses.

Statistical analyses

First, SL scores were compared to scores obtained by the control group using the modified t-tests (J. R. Crawford & Howell, 1998) with one-tail (as SL scores were expected to be below the scores of the controls) and alpha at .05. We used the Singlims program, specifically developed to assess whether single case scores differ

significantly from a control sample (J.R. Crawford & Garthwaite, 2002). Second, the differences in scores obtained in recall of past and generation of future event details was compared using the DiffBayes.exe program (J. R. Crawford & Garthwaite, 2007). This program, based on Bayesian approach, was developed to compare differences between scores on two tasks obtained by a single case with the differences between scores obtained on the same two tasks obtained by a control group. It provides: probability (p value) and estimate of the "percentage of the control population that would exhibit a more extreme discrepancy" (Crawford & Garthwaite, 2007, p 365) than a single case. Both programs were accessed through Professor Crawford's web-page: http://homepages.abdn.ac.uk/j.crawford/pages/dept/psychom.htm.

Results

Past and future thinking: Adapted Autobiographical Interview

As can be seen in Figure 3, SL recalled no specific events from the past two weeks or past two years. Modified t-tests showed that her scores (RSs = 0) differed significantly from controls [n = 11, comparable in age M=48.27 years (SD=6.65) and education M=16.18 years (SD=1.99)], for both internal and external details provided in specific events that happened over the (i) past two weeks [$t(10)$=-3.69, $p=0.002$, Z-$CC = -3.857$ and $t(10)$=-2.57, $p=0.014$, Z-$CC = -2.680$ respectively] and (ii) past two years [$t(10)$=-4.84, p<0.001, Z-$CC = -5.053$ and $t(10)$=-2.93, $p=0.008$, Z-$CC = -3.062$, respectively].

In contrast, SL generated specific future events. The number of internal and external details provided by SL and control participants did not differ [next few weeks ($t(10)$=-0.37, $p=.179$, Z-$CC = -0.389$ and $t(10)$=-1.04, $p=0.081$, Z-$CC = -1.083$ respectively), next few years ($t(10)$=-0.53, $p=0.151$, Z-$CC = -0.556$ and $t(10)$=-0.98, $p=0.087$, Z-$CC = -1.027$ respectively))]. Moreover, the Bayesian tests revealed that the difference

14

between past and future internal (but not external) details was significantly greater for SL relative to controls ($p<.001$; *Z-DD* = -4.759 and $p=.368$; *Z-DD* = -0.403). The likelihood that the difference between the number of past and future internal details for a control participant would be greater than that of SL was 0.00079.

----- Figure 3 -----

Example transcripts of past and future proximal and distal event descriptions provided by SL and by one of the control participants are given below (Figure 4 a) and b), respectively). As can be seen, SL's description of a future holiday event was detailed, vivid and well organised, but she cannot recall any specific events from the past two years. There was no evidence of confabulation in the events she generated, all were considered plausible.

----- Figure 4 -----

Analysis of the phenomenological details was not conducted for past events, as SL had not recalled any information. As can be seen in Table 2, SL's ratings of future events provided for the next two weeks and next two years were similar to ratings provided by control subjects in terms of (i) emotional impact and (ii) personal significance. Similarly, there was no significant difference between SL and control subjects in their ratings of the vividness of distal future events. However, compared to the control group, SL rated her proximal future event descriptions (next two weeks) as being of significantly lower vividness. Next, two research staff members (blinded to the participants' group membership) rated the vividness and contiguity of the transcribed future events provided by SL and control participants. Vividness and

Into the future with little past

contiguity ratings of SL's proximal and distant future events made by the research

staff were comparable to that of control participants.

----- Table 2 -----

3.2 Memory for the past: Autobiographical Interview

As shown in Figure 5, SL provided a significantly smaller number of internal details

from the more recent (middle age: $t(17)=-3.21$, $p=0.003$, $Z\text{-}CC = -3.294$ and last year:

$t(17)=-3.53$, $p=0.001$, $Z\text{-}CC = -4.301$), but not distant (teenage $t(17)=0.42$, $p=0.340$,

$Z\text{-}CC = 0.428$ and early adult $t(17)=0.70$, $p=0.247$, $Z\text{-}CC = 0.717$) life periods relative

to a group of control subjects of similar age and education [n=18; age M = 45.3 (SD

=4.9); education M = 12.8 (SD = 3.4)]. SL and control subjects generated comparable

numbers of external details across the three earlier life periods: teenage ($t(17)= 0.35$,

$p=0.364$, $Z\text{-}CC = 0.362$), early adult ($t(17)=-0.24$, $p=0.405$, $Z\text{-}CC = -0.250$) and

middle age ($t(17)=1.40$, $p=0.089$, $Z\text{-}CC = 1.441$) Similar to the findings on the

adapted AI, for the most recent year, SL's recall of external details from an event was

impaired ($t(17)=-1.84$, $p=0.04$, $Z\text{-}CC = -1.889$).

----- Figure 5 -----

Discussion

To our knowledge, this is the first study that examined future thinking in a patient

(SL) with severe WKS amnesia and volumetric confirmation of bilateral mammillary

body damage with relatively preserved hippocampi and anterior thalamic nuclei.

Although SL had substantial (albeit temporally limited and temporally graded)

deficits in episodic memory in general, she was able to imagine fictitious, but

plausible, future experiences of comparable richness and with similar

16

phenomenological qualities to those of controls. This was at odds with our prediction and with the findings for the majority of patients with adult-onset amnesia secondary to medial temporal lesions.

Unlike all other amnesia cases with selective lesions of the Papez circuit in which future thinking has been investigated, SL had only limited hippocampal atrophy, but instead bilateral mammillary body and fornix damage. To date, the only other study that examined past and future thinking in patients with diencephalic damage involved two stroke cases with lesions of the medial-dorsal thalamus (Weiler, Suchan, Koch, Schwarz, & Daum, 2011). The patients in that study were free of anterograde memory deficits, had intact recall of events from the past and showed only very mild deficits in future thinking. The discrepancy between our findings and the results of Weiler and colleagues can be attributed to the differences in the diencephalic structures involved and their connectivity. Patients with lesions involving the medial-dorsal thalamus were specifically selected by Weiler et al. (2011) because of the strong connection this nucleus has to the prefrontal cortex (Johansen-Berg et al., 2005). The medial-dorsal thalamus does not receive any direct afferents from the hippocampus. Thus it is not surprising that the two patients examined by Weiler and colleagues showed deficits in executive skills, but only very mild anterograde memory deficits. By contrast, SL's lesions in the mammillary bodies and fornix, which receive their main input fibres from the hippocampus (Aggleton et al., 2010; Vann, 2010), produced a severe amnestic syndrome, but little deficits in executive skills. Thus, the divergent findings of the two studies with respect to future thinking are likely explained by the difference in the anatomical connectivity of the lesioned regions and the opposite pattern of preserved and impaired cognitive skills. It seems likely that damage to the links between the thalamus and frontal cortices (and

associated deficits in executive skills) as a result of stroke in the medial-dorsal nucleus may have resulted in the subtle deficits in future thinking reported in the cases reported by Weiler et al. (2011). In contrast, relatively preserved executive skills could have supported SL's ability to generate future events by utilising established event-scripts stored in semantic memory or from the preserved, distant events.

The discrepancy between SL's past recall deficits and relatively intact future thinking was striking. Such discrepancy is typically not found in patients with adult onset anterograde and retrograde amnesia, when amnesia is secondary to bilateral medial temporal lesions (MC in Andelman et al., 2010; 4 out of 5 cases in Hassabis et al., 2007; DB in Klein, Loftus & Kihlstrom, 2002; 8 patients in Race, Keane & Verfaelli, 2011; NN later named KC in Tulving, 1985 and Rosenbaum et al., 2005). Although Squire et al. (2010) and Hassabis et al. (case PO1, 2007) reported a pattern similar to SL's in several cases with adult onset amnesia, in these cases, the reduction in hippocampal volume was extreme (i.e., in excess of 3 standard deviations from the control mean in the case reported by Squire et al., 2010 and greater than 40% in Hassabis et al case PO1. In SL, bilateral hippocampal volume was slightly (1.09 standard deviations), but not significantly, reduced relative to controls. While this raises a possibility that SL experienced some hippocampal volume loss as a result of her illness, the severity of her memory deficits greatly exceeds memory deficits that are likely to arise form a possible mild reduction in hippocampal volume. Instead, her memory deficits are attributable to the significant volume changes evident in her mammillary bodies and fornix. Although an association between amnesia and mammillary body lesions has been known for a long time (Gudden, 1896), the contribution of this diencephalic structure to memory is still being discussed (Vann, 2010) and the specific contributions that the mammillary bodies make to future

thinking had not been previously investigated. Their small size makes it difficult to detect significant activations with fMRI. Indeed, the mammillary bodies are often seen merely as a relay station between the hippocampus and the anterior thalamus, as they do not comprise interneurons, which usually allow excitatory or inhibitory modulation of neural signals (Aggleton et al., 2010; Vann, 2010). Still, the medial nuclei of the mammillary bodies, which are always affected in WKS (Kopelman, 1995), receive input from multiple regions (i.e., hippocampus, tegmentum, prefrontal cortex). Convergence of these inputs appears to be critical for intact retrieval of contextual-rich information (see also Tsivilis et al., 2008). Our findings confirm that the mammillary bodies and fornix are critical for retrieval of contextually rich autobiographical memories, but they play little role in future thinking. This contrasts with the role of the hippocampus, which seems to be involved in both processes (Andelman et al., 2010; Hassabis et al., 2007; Klein et al., 2002; Race et al., 2011; Rosenbaum et al., 2005; Tulving, 1985; though see Squire et al., 2010 for some cases of adult-onset hippocampal amnesia without deficits in future thinking). These findings imply that both past and future event thinking share only a subset of brain regions, including the hippocampus, and although past event retrieval requires additional processing in diencephalic brain regions, future thinking does not.

The dissociation of past and future thinking that we observed in our case study seems to contradict the constructive episodic simulation hypothesis (Schacter & Addis, 2007; Schacter, Addis, & Buckner, 2007) and findings that the amount of episodic details (Addis & Schacter, 2008) drops in both past and future event descriptions as temporal distance from the presence increases. Indeed, according to this hypothesis, there should be a clear correlation between recalled details of past events and the generation of future events, but instead, we found a severe impairment

limited to the description of past events. Not only were SL's descriptions of future events comparable to those of NC subjects in terms of quantity of internal and external details, although her scores are somewhat below the mean scores of control subjects, but also in most of the phenomenological ratings. Only SL's self-ratings of vividness of proximal future memories were lower than those of control subjects. The transcripts of these events were rated (by an independent judge) as being of comparable vividness as the events described by control subjects. Thus the significance of SL's lower rating of vividness of her proximal future event is unclear, but will be considered in our future studies. Her ratings of the emotional impact and personal significance of the future events generated fell within normal limits. Previous findings in WKS patients indicate that some very remote autobiographical memories remain intact (Kopelman, 1989; Kopelman et al., 1999), which is consistent with our findings of preserved episodic memories for teenage and early adulthood years in SL. It is possible that when creating future scenarios, SL utilised distant, preserved episodic memories to compensate for the episodic memory loss that covered some 15-20 years of her life, an issue we are currently investigating. This is further corroborated by her clinical notes which showed that her episodic present time was situated well and truly in the past. We propose that lesions in non-hippocampal regions of the Papez circuit regions do not affect the simulation of future events, because patients can either rely on the retrieval of very remote autobiographical memories and/or utilise established event-scripts stored in semantic memory as scaffoldings to create future events.

It will be critical to corroborate these findings in a bigger sample of patients in the future. Case studies are often viewed as controversial as it is not clear whether the examined patient is representative for effects on a population level.

Into the future with little past

Nevertheless, our findings replicate previous autobiographical memory findings in patients with WKS and the neuroimaging profile was very clear cut, which suggests that the findings in this study are genuine. Taken together, our results suggest that mammillary body and fornix damage specifically impaired anterograde memory and recall of autobiographical memories from the past several years, but not projections of future events. This dissociation suggests that the hippocampus may be critical for both processes while non-hippocampal diencephalic structures are only involved in the retrieval of the past. From the cognitive perspective, dissociation between past and future events found in our study, but also in two other studies that involved patients with anterograde amnesia and retrograde memory deficits (temporally extensive, PO1 in Hassabis et al., 2007 and temporally graded, 6 cases in Squire et al., 2010) are at odds with the constructive episodic hypothesis, which suggests that construction of future events involves a single cognitive route: recollection of past events from which episodic details are sourced and recombined to construct future events via relational processes (i.e., relational memory). Thus we purport that an alternative cognitive and anatomical route enables patients with impairments in relational memory and autobiographical episodic memory to imagine and describe future events. In particular, preserved executive skills might allow one to draw on event-scripts stored in semantic memory to construct future events. Anatomically, a potential split of pre-versus post-commissural fornix projections from the hippocampus could explain the dissociation of the functions. More specifically, only post-commissural fornix fibers project to the mammillary bodies whereas pre-commissural fibres project to medial prefrontal cortex regions (Vann & Aggleton, 2004), which has been shown to be critically involved in future thinking (Stawarczyk & D'Argembeau, 2015). Hence it is possible that SL was able to construct future events because her hippocampus and

frontal lobes were still able to work together even though (because of a mammillary body lesion) she was unable to form new relational memories. Further experimental studies examining dissociations and exceptional cases in general as well as clinical populations are likely to provide further insight into cognitive architecture of future thinking, and refine theories.

Disclosure

No financial interest or benefits have been gained or are expected to be gained from the applications of this research.

Figure Legends

Figure 1. Magnetic Resonance Imaging (MRI) scan showing SL's lesions in the

mammillary bodies compared to a healthy control.

Figure 2. Regions of interest (hippocampus, fornix, mammillary bodies, anterior

thalamus) volumes in SL and controls. Line indicates mean volume in controls.

Figure 3. Mean number of internal and external event details for SL and controls for

adapted AI divided with respect to temporal distance (weeks, years) and direction

(past, future). Error bars represent standard error of the mean.

Figure 4. Transcripts of proximal (a) and distal (b) past and future event descriptions

provided by SL and a control participant on the adapted AI.

Figure 5. Mean number of internal and external event details for SL and controls

obtained on AI. Error bars represent standard error of the mean.

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