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The GABA_B receptor agonist, baclofen, contributes to three distinct varieties of amnesia in the human brain – a detailed case report

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SUMMARY

We describe a patient in whom long-term, therapeutic infusion of the selective gamma-amino-butyric acid type B (GABA_B) receptor agonist, baclofen, into the cerebrospinal fluid gave rise to three distinct varieties of memory impairment: i) repeated, short periods of severe global amnesia, ii) accelerated long-term forgetting, evident over intervals of days and iii) a loss of established autobiographical memories. This pattern of impairment has been reported in patients with temporal lobe epilepsy, in particular the subtype of Transient Epileptic Amnesia. The amnesic episodes and accelerated forgetting remitted on withdrawal of baclofen, while the autobiographical amnesia persisted. This exceptional case highlights the occurrence of 'non-standard' forms of human amnesia, reflecting the biological complexity of memory processes. It suggests a role for GABA_B signalling in the modulation of human memory over multiple time-scales and hints at its involvement in 'epileptic amnesia'.

1. Introduction

The complexity of the biochemical, cellular and network mechanisms implicated by neuroscience in memory processing predicts corresponding forms of human memory disorder. These are likely to defy the monolithic concept of ‘long-term memory’ familiar from classical psychology. Examples have recently come to light in studies of patients with the most common form of adult-onset epilepsy, temporal lobe epilepsy (TLE), particularly the subtype known as transient epileptic amnesia (TEA) (Zeman & Butler, 2010). Patients with TEA typically present with a triad of non-standard memory impairments: i) repeated, short periods of severe global amnesia, ii) persistent accelerated long-term forgetting (ALF) – the loss of newly acquired, initially accessible, memories over hours to weeks, and iii) a permanent loss of remote, established, autobiographical memories. Here, we report a detailed study of a patient who developed precisely this pattern of memory impairment in the context of therapeutic infusion of baclofen, a selective agonist at the GABA_B receptor, into the cerebrospinal fluid (CSF).

Baclofen is a widely-used therapy for ‘spasticity’, the increase in muscle tone and tendon reflexes, sometimes accompanied by painful spasms, which can result from lesions of the descending corticospinal tracts. It can be given orally, or, in more severe cases, by infusion from an implanted pump into the CSF (Hsieh & Penn, 2006). This targets the drug on the desired spinal site of action, but the normal bulk flow of CSF toward the brain sometimes leads to CNS side-effects (Kofler, Kronenberg, Rifichi, Saltuari, & Bauer, 1994). In overdose, intrathecal baclofen can cause coma and status epilepticus (Nugent, Katz, & Little, 1986; Saltuari, Marosi, Kofler, & Bauer, 1992). Memory disturbance has been described occasionally in patients taking baclofen (Sandyk & Gillman, 1985), including reports, with very limited neuropsychological detail, of two patients with discrete, recurrent episodes of

memory loss in the context of intrathecal baclofen treatment (Grande, Loeser, & Samii, 2008; Rosenblum & Desan, 2014) This association between baclofen and memory impairment is in keeping with the crucial role of the GABA_B receptor, at which baclofen is a selective agonist, in memory processing (Gassmann & Bettler, 2012).

GABA, the main inhibitory neurotransmitter in the human nervous system, acts at both ionotropic (GABA_A) and metabotropic (GABA_B) receptors. In the context of memory, close interactions between GABA_B receptors and the glutamatergic system, involving pre- and post-synaptic effects, maintain a favourable 'dynamic range' for memory processing at synapses in the hippocampus and neocortex. The GABA_B receptor has been implicated in both the short and longer term control of memory, through effects on early and late synaptic events: the former include early phases of long-term potentiation and depression (Davies, Starkey, Pozza, & Collingridge, 1991), the latter processes of synaptic growth and retraction involving crucial regulatory proteins such as cyclic adenosine monophosphate response element-binding protein (CREB) (White et al., 2000) and brain-derived neurotrophic factor (BDNF) (Khundakar & Zetterstrom, 2011). Activation of the GABA_B receptor in experimental studies in animals has predominantly, though not exclusively, inhibitory effects on memory processing (Gassmann & Bettler, 2012).

Although the combination of epilepsy and memory disturbance has been described in the recently recognised syndrome of limbic encephalitis associated with antibodies to the GABA_B receptor (Lancaster et al., 2010), we did not suspect a link between GABA signalling and the features of TEA until we were contacted by MK and CS. Encountering our project website (<http://projects.exeter.ac.uk/time/>), they were struck by the similarities between CS'

symptoms and those described in TEA. We conducted a series of tailored experiments ON baclofen and OFF baclofen to explore the nature of CS' amnesia under controlled conditions.

2. Methods

2.1 Participants

In Experiments 1-3, control participants were healthy individuals (1m/8f) matched for age and education with CS (see supplementary data for full details of basic psychometric data and Methods). There were no significant differences between CS and control participants on standard measures of intelligence (Wechsler Abbreviated Scale of Intelligence Scale (WASI) similarities, matrix reasoning), visual memory (Rey figure delayed recall), or executive function (verbal fluency) either ON or OFF baclofen. There was a trend toward a reduction in delayed story recall ($p = 0.09$) in CS when tested ON baclofen. CS' depression rating on the Hospital Anxiety and Depression Scale (HADS) was elevated at the time of testing ON baclofen ($p < 0.002$). In Experiment 4, CS' scores were compared to those obtained from 12 healthy, age and IQ matched control participants whom we have previously reported (Milton et al., 2010). There were no significant differences between CS and these control participants on standard measures of verbal memory (immediate and delayed story recall), visual memory (Rey figure delayed recall), or executive function (verbal fluency) either ON or OFF baclofen. There was a trend toward an elevation of anxiety in CS when tested ON baclofen ($p = 0.062$). Her depression rating on the HADS was elevated both ON and OFF baclofen ($p = 0.002$ ON, 0.020 OFF). Informed consent was obtained from all participants with approval by appropriate Ethics Committees.

2.2 Experiments

CS had no episodes of transient amnesia during the two week-long periods of testing described below.

2.2.1 *Experiment 1: word list recall and recognition*

We probed CS' verbal memory ON and OFF baclofen using four categorical 16-word lists, entitled "Animals", "City", "Nature" and "Groceries" (Hoefeijzers, Dewar, Della, Butler, & Zeman, 2014). Two were used ON baclofen and two OFF baclofen. Controls were tested at the same inter-test interval (~ one year). Two learning trials were given of each visually-presented list, with recall immediately after each trial, at 30 minutes and at one week. Recognition was assessed following free recall at one week, using a 64-item yes/no test, comprising the 32 target words and 32 foils.

2.2.2 *Experiment 2: visual recognition memory*

We probed CS visual memory using 400 complex colour photos (sourced from Getty Images) depicting everyday-life scenes and activities (Dewar, Hoefeijzers, Zeman, Butler, & Della Sala, 2015). 200 were used for the ON baclofen test, the remaining 200 for the OFF baclofen test. Different subsets of stimuli were probed after 30 min and 1 week. Controls were tested at the same interval as CS. On each occasion, 120 pictures were studied sequentially for 4 seconds each. Recognition memory was tested at 30 minutes and 1 week using 40 photos from the original 120 photos (i.e. targets), 20 photos closely resembling 20 of the original photos (i.e. similar foils) and 20 dissimilar foils.

2.2.3 Experiment 3: incidental learning

The experimenter told an apparently casual but well-rehearsed story during a prearranged interval in testing. This consisted of 51 story points. Retention was probed without warning one week later, first via free recall, followed by a 5-alternative forced-choice recognition test, consisting of 13 questions. We used the same story ON and OFF baclofen.

2.2.4 Experiment 4: autobiographical memory

We investigated CS' autobiographical memory using an exacting measure designed to distinguish the 'episodic' or 'internal' details which are evoked when we re-experience past events, relating to action, place, time, perception, thought and emotion, from 'semantic' or 'external' details (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002). ON baclofen, CS retrieved a unique autobiographical memory from each decade of her life. General and specific probes were used to elicit all available details. OFF baclofen (~ 1 year later) CS retrieved the memories volunteered at the first session ('repeated' memories), and a new memory from each decade ('new' memories). The memories were audio-recorded, transcribed and scored using standard procedures (Levine et al., 2002).

2.3 Statistical analysis

Percentage retention scores, hit and false alarm (FA) rates and d-prime (d') scores were calculated using standard methods (see supplementary data). We used Crawford's modified t-tests for single case studies (singlims (Crawford & Garthwaite, 2002); RSDT (Crawford & Garthwaite, 2005)) to compare CS' scores and her change in performance from ON to OFF baclofen with equivalent values in controls. T-tests were two tailed apart from the ON baclofen 1-week t-tests for free recall and autobiographical memory for which we had a directional prediction, based on CS's specific report.

3 RESULTS

3.1 Case report

CS, a University educated, 52 year old, female, business executive, developed pain from spinal scoliosis in 2005. She underwent initial surgical procedures in 2006 and 2008. During a third procedure in 2009 she suffered an incomplete spinal cord injury which left her paralysed from the chest down. Apart from her scoliosis, CS had no history of previous hospital admissions, chronic disorders, unexplained symptoms or surgery. There was no past history of psychological distress or psychiatric disorder. She was a highly independent person, had travelled widely in her professional role and enjoyed an active social life. She was married, with one child. Following the injury to her spinal cord in 2009, CS developed painful and debilitating spasticity affecting her legs and torso. CS became depressed and was treated with Sertraline in 2009, to good effect. She continued to take this drug, at a dose of 100-150 mgs/day, throughout the period described below. An intrathecal baclofen pump was inserted in 2010. Control of symptoms required an increasing dose. During the second quarter of 2011, on a rising dose of baclofen (Figure 1), CS noted a deterioration of her previously excellent memory, as attested by her family and friends. In particular, she found that newly-formed memories faded rapidly over days to weeks. This 'delayed' forgetting differs markedly from classic anterograde amnesia, characterised by forgetting of new information over seconds. She also found herself unable to 're-experience' remote events, like foreign holidays or business trips, which she could previously recollect without difficulty, and it became hard to visualise once familiar routes around her neighbourhood. In June 2011, CS had the first of many brief amnesic episodes. Lasting from a few minutes to half an hour, these were characterised by both difficulty in recalling prior events and in laying down a memory for ongoing events. CS had ~30 such episodes while on a high dose of baclofen (see

Figure 1). Following dose reduction, they ceased almost completely for around 2 months, but after a small increase, they returned. A psychiatrist suggested that they were ‘dissociative’. At around this time CS referred herself into our study. Structural MRI scanning of the brain was normal. Investigation for epilepsy with standard and sleep deprived EEG recording gave negative results. There was no positive response to anticonvulsant treatment with Lamotrigine at a near maximal dose of 400 mgs/day. It was discontinued after 6 months. CS had a further ~140 episodes of amnesia before withdrawing from baclofen, at our suggestion. Following this, the amnesic episodes and ALF stopped altogether. She has since resumed low-dose baclofen therapy without recurrence of her amnesic episodes or symptoms of ALF, though her remote memory impairment has persisted.

3.2 Experiment 1: word list recall and recognition

CS’ immediate recall, learning rate and percentage retention at 30-min free recall were similar to those of the controls ON and OFF baclofen (Figures 2a,b, c: all $p > .123$). In contrast, her percentage retention at 1-week free recall was impaired ON baclofen ($p = .028$) but not OFF baclofen ($p = .276$ – Figures 2c,d). Relative to the controls, CS had severe ALF ON ($p = .004$) but not OFF baclofen ($p = .544$). Her improvement in 1-week word retention from ON to OFF baclofen was significantly larger than the change in performance over the equivalent time period in controls ($p = .021$). Her 1-week word recognition (d' score – Figure 3) was marginally reduced ON baclofen ($p = .065$) but not OFF baclofen ($p = .891$: see supplementary data for a full statement of the results). This reduction was attributable to an elevated FA rate ON baclofen ($p=.019$).

3.3 Experiment 2: visual recognition memory

Figure 4 shows recognition performance for real-life photos after 30 min and 1 week in CS and controls. ON baclofen, CS had a significantly elevated rate of FAs after the 30-min delay

($p = .023$) and after the 1-week delay ($p = .041$). Her d' score was below that of the poorest performing control after both delays, with a trend towards statistical significance (30 min: $p = 0.1$; 1 week: $p = .076$). CS' overall picture recognition performance OFF baclofen was comparable to that of the controls, although her FA rate continued to be mildly raised after the 1-week delay ($p = .083$). The improvement in her 1-week picture recognition d' from ON to OFF baclofen was larger than the change in d' over the equivalent time period in controls, ($p = .062$). CS had no difficulty in discriminating between perceptually similar photos after a short delay (900ms), either ON or OFF baclofen (see supplementary data).

3.4 Experiment 3: incidental learning

CS' 1-week memory of the story was marginally impaired ON baclofen (Figure 5: free recall: $p = .066$; forced choice recognition: $p = .061$). OFF baclofen, her memory of the story was similar to that of the controls ($p = .566$ for recall, $.598$ for recognition; Figure 5b). CS's improvement in recognition memory performance from ON to OFF baclofen was marginally larger than the change in performance over the equivalent time period in controls ($p = .063$).

3.5 Experiment 4: autobiographical memory

ON baclofen, CS had a lower overall autobiographical memory quality than controls ($p < .001$). Memory was impaired for four of the six decades of her past life, sparing her thirties and the most recent decade (Figure 6a,b). The recent, spared, memory concerned her 50th birthday celebration, four months before the test session. OFF baclofen, overall memory quality was reduced across the life-span, both for 'repeated' and 'new' memories (both $p < .001$; Figure 6c,d). On this occasion she also supplied a lower mean number of internal details ($p = .033$). The rich memory of her birthday party had degraded markedly, a rare, prospective demonstration of 'retroactive' loss of a well-established memory.

4 Discussion

4.1 Main findings

These findings suggest that the GABA_B agonist, baclofen, can induce a distinctive and unusual pattern of memory impairment, including recurrent episodes of profound, transient amnesia, ALF, an early deficit of visual recognition memory and autobiographical amnesia (AbA). Remarkably, this is precisely the pattern of memory impairment recently reported in the syndrome of TEA (Zeman, Butler, Muhlert, & Milton, 2013; Hoefeijzers et al., 2014; Dewar et al., 2014; Milton et al., 2010). In CS's case the transient memory impairment and ALF resolved with withdrawal of baclofen, while her AbA has persisted.

4.2 What caused the episodes of transient amnesia?

Transient amnesia is a common neurological symptom (Bartsch & Butler, 2013). Its differential diagnosis includes post-traumatic, transient global (TGA), transient epileptic, transient ischaemic, psychogenic, migrainous and drug-induced variants (see Table 1). Although the link between CS' baclofen treatment and her transient amnesic episodes is clear, the mechanism by which baclofen caused them is not. Two previous case reports have assumed that baclofen can cause TGA (Grande et al., 2008; Rosenblum & Desan, 2014). This is possible, though the brevity and frequency of episodes in these cases would be unusual for TGA (Bartsch & Butler, 2013). Baclofen is capable of provoking both generalised and focal seizures, making an epileptic mechanism plausible (Han, Cortez, & Snead, 2012; Kofler et al., 1994). The lack of associated symptoms of epilepsy, EEG abnormalities or response to anticonvulsant treatment, argue somewhat against this diagnosis in CS' case. We discuss the analogies between CS' case and the features of TEA further below.

4.3 The neural basis of ALF

Between her frequent episodes of transient amnesia, CS' memories showed a conspicuous tendency to fade over days, as documented by our word recall results ON baclofen (see Figure 2). This was not caused by the amnesic episodes per se: the marked impairment of verbal recall one week occurred in the absence of any discrete amnesic events.

ALF, the accelerated loss over longer intervals of information which can be retrieved normally over standard intervals, has been described most often in patients with temporal lobe epilepsy, especially transient epileptic amnesia (Elliott, Isaac, & Muhlert, 2014). The occurrence of ALF, in any context, raises two key theoretical questions. First, does it result from a fragility of the initial memory trace, which only becomes apparent after a delay, or from an impairment of memory consolidation? We suspect that in CS's case, and probably in patients with epilepsy as well, both are relevant. While CS' subjective complaint was of fading of memories over days, as documented using our test of verbal recall, there was also evidence, from our demanding measure of visual recognition memory, for subtle impairment of memory over shorter intervals (see Figure 4). Recent evidence from animal studies points to a key role for GABA_B signalling in the maintenance and consolidation of memories over delays (Cullen, Dulka, Ortiz, Riccio, & Jasnow, 2014) via mechanisms including sharp wave-ripples (Hollnagel, Maslarova, Haq, & Heinemann, 2014), immediate-early gene expression (Terunuma et al., 2014) and, possibly, neurogenesis (Giachino et al., 2014). The likelihood that 'recurrent rounds of consolidation-like events' (Bekinschtein et al., 2007, p261) are required to maintain memory traces in the hippocampus predicts a progressive weakening of memories in the presence of an agent, such as baclofen, that reduces the effectiveness of each iteration.

The second key theoretical question is whether ALF results from a structural pathology of the episodic memory system or can be caused by a purely physiological – and therefore fully reversible – disturbance. There have been reports of improvement or resolution of ALF on treatment of seizures (Midorikawa & Kawamura, 2007; O'Connor, Sieggreen, Ahern, Schomer, & Mesulam, 1997), supporting a physiological explanation, but ALF often persists in patients whose clinical seizures have ceased (Butler et al., 2007). CS's case shows unequivocally that a fully reversible, pharmacological, effect is capable of causing ALF.

While the effect of baclofen was evidently reversible, we cannot be certain of the anatomical site primarily involved. The hippocampus is a plausible candidate, given its high density of GABA_B receptors (Osten, Wisden, & Sprengel, 2007), proximity to the CSF and involvement in TEA (Butler et al., 2013) and related disorders. However other structures, such as the septal nuclei (Moor, DeBoer, & Westerink, 1998; Turi, Wittmann, Lechan, & Losonczy, 2015) and thalamus (Tu, Miller, Piguet, & Hornberger, 2014), could also have played a role.

4.4 The neural basis of autobiographical amnesia

In contrast to the reversibility of CS' ALF, her AbA has persisted. A similar dissociation has been described in a patient with TEA (Midorikawa & Kawamura, 2007). Taken together, these findings suggest that factors giving rise to repeated episodes of transient amnesia can render previously established memories persistently inaccessible or delete them altogether. The prospective demonstration of such a 'vanishing memory' in the case of CS' 50th birthday memory is striking.

Examples of selective or 'disproportionate' AbA, due to brain disease, in patients with preserved anterograde memory at standard delays, are rare and sometimes controversial

(Kopelman MD, 2004; Markowitsch & Staniloiu, 2013), but there are other well documented examples. Such cases suggest that selective Aba can arise from a range of different pathologies, including i) diffuse pathology (Evans JJ, Breen EK, Antoun N, & Hodges JR, 1996; Evans, Graham, Pratt, & Hodges, 2003), ii) right temporofrontal pathology (Levine B et al., 1998; Levine, Svoboda, Turner, Mandic, & Mackey, 2009), iii) visual cortical pathology (Rubin & Greenberg, 1998), iv) temporal lobe epilepsy (Tramoni et al., 2011; Jansari, Davis, McGibbon, Firminger, & Kapur, 2010; Hornberger et al., 2010; Butler et al., 2007) as well as v) functional or dissociative amnesia (Staniloiu & Markowitsch H, 2014; Markowitsch & Staniloiu, 2013) and the recently described syndrome of ‘severely deficient autobiographical amnesia in healthy adults’ (Palombo, Alain, Soderlund, Khuu, & Levine, 2015). This wide range of potential causes might be predicted from the existence of a complex network subserving autobiographical memory (Svoboda, McKinnon, & Levine, 2006). While the possibility of dissociative amnesia, considered further below, clearly deserves consideration in a case such as CS’, with marked autobiographical amnesia and a degree of mood disturbance, the growing understanding of the range of neurological causes for Aba has enlarged the differential diagnosis (Staniloiu & Markowitsch H, 2014).

4.5 Analogies with transient epileptic amnesia

The close similarities between the memory disorders induced in CS by baclofen and the clinical phenotype of TEA raise the possibility that disturbances in GABA_B signalling are involved in TEA. Shared features include the episodes of dense transient amnesia, background of persistent ALF, lasting, remote AbA and visual recognition memory impairment (Dewar et al., 2015; Zeman & Butler, 2010). In particular, CS’ case suggests the testable hypothesis that ALF in TEA might be due to an up-regulation of GABA_B signalling. Altered expression of GABA_B receptors has been described in the hippocampus of patients

with TLE (Furtinger, Pirker, Czech, Baumgartner, & Sperk, 2003; Munoz, Arellano, & DeFelipe, 2002) and GABA_B receptors are functionally upregulated in epilepsy-prone lethargic (Ih/Ih) mice (Hosford et al., 1992).

4.6 The possibility of ‘psychogenic amnesia’

Several features of CS’ case might raise suspicion of a ‘psychogenic’, ‘dissociative’ or ‘functional’ form of amnesia (see Table 1). Functional amnesia classically affects autobiographical memory and has been described as a rare cause of ALF (Markowitsch & Staniloiu, 2013; Staniloiu & Markowitsch H, 2014). Her spinal cord injury was a severely stressful life event. In its aftermath she became depressed and was treated with an antidepressant, Sertraline. When tested ON baclofen, while CS no longer satisfied criteria for major depression, her HADS score (12) placed her just within the abnormal range (11-21 – although this score was probably inflated by her neurological symptoms).

However, CS’s case fully satisfies only one of the six criteria suggested by Markowitsch and Staniloiu (Markowitsch & Staniloiu, 2013) as supportive of a diagnosis of ‘functional retrograde amnesia’, namely the relationship of the onset to psychological trauma or stress. The other criteria comprise: i) selective retrograde amnesia, ii) loss of personal identity, iii) absence of a physical or medical cause for amnesia; iv) prior history of psychological trauma or mood disorder; v) belle indifference. With the partial exception of CS’ recent, successfully treated, reactive depression, her case does not satisfy these five criteria. The absence of these features, together with the distinctive pattern of CS’ amnesia (see 4.5), and the resolution of her amnesic episodes and ALF on withdrawal of baclofen, argue strongly for a pharmacological rather than a psychological explanation for her memory symptoms.

4.7 Pharmacological complexity

CS' complex amnesic syndrome developed on treatment with an increasing dose of baclofen and resolved once baclofen was withdrawn, suggesting a direct relationship. However, throughout the period of treatment with baclofen, CS also received the selective serotonin reuptake inhibitor (SSRI), sertraline. As this drug was started prior to the onset of her amnesic syndrome and withdrawn after it had resolved, sertraline cannot be the primary cause. Could it, however, have acted in concert with baclofen? There are well-established interactions between serotonin and GABA in the medial temporal lobes. In particular, acute treatment with the SSRI paroxetine causes a transient decrease in BDNF gene expression which is mediated by GABA_B receptors (Khundakar & Zetterstrom, 2011). Prolonged treatment with SSRIs, however, appears likely to increase BDNF gene expression, an effect which may be relevant to their antidepressant action (Khundakar & Zetterstrom, 2011). Thus, while an interaction between baclofen and sertraline may have contributed to CS' amnesic syndrome, the known pharmacology of the SSRIs suggests that this is unlikely.

4.6 Conclusion

CS's case demonstrates that intrathecal baclofen, a GABA_B receptor agonist, can cause or contribute to a transient amnesic syndrome associated with accelerated long-term forgetting and autobiographical amnesia. It suggests that GABA_B signalling plays a vital role in human memory, modulating memory processes over multiple time scales of minutes, days and years, that transmission at the GABA_B receptor is relevant to syndromes of transient amnesia in humans, and that therapies directed at this target deserve consideration.

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Figure legends**Figure 1**

Baclofen dose (micrograms/day), attack frequency (/month) and Lamotrigine dose (mgs/day) in patient CS over time (Feb 2010 – April 2014).

Figure 2

Experiment 1a: number of words recalled at learning trials 1 and 2 (**2a, b**), and percentage word retention after 30 minutes and 1 week (**2c, d**) ON baclofen and OFF baclofen in CS and at equivalent test times (first test and second test) in 9 controls. Bars indicate +/- 1 standard deviation.

Figure 3

Experiment 1b: 1-week word recognition performance ON baclofen and OFF baclofen in CS and at equivalent test times (first test and second test) in 9 controls. **3a, b** show d' , **3c, d** hit rate and false alarm rate. Bars indicate +/- 1 standard deviation.

Figure 4

Experiment 2: 30-minute and 1-week picture recognition performance ON baclofen and OFF baclofen in CS and at equivalent test times in 9 controls. **4a, b** show d' , **4c, d** hit rate, **4e, f** false alarm rate. Bars indicate +/- 1 standard deviation.

Figure 5

Experiment 3: 1-week free recall (proportion correct) and 5-alternative forced-choice recognition (proportion correct) of an incidentally-encoded 'everyday life' story, ON

baclofen and OFF baclofen in CS (**5a**) and at equivalent test times (first test and second test) in 8 controls (**5b**). Bars indicate +/- 1 standard deviation.

Figure 6

Experiment 4: internal details and overall memory quality ratings for each decade of life, ON (**6a, b**) and OFF baclofen (**6c, d**) in CS and in 12 control participants. Bars indicate +/- 1 standard deviation.

Table legends

Table 1

The clinical features of transient amnesic syndromes: Transient Global Amnesia (TGA), Transient Epileptic Amnesia (TEA), Transient Ischaemic Amnesia (TIA) and Functional (or Dissociative or Psychogenic) Amnesia.

Reference List

- Bartsch, T. & Butler, C. (2013). Transient amnesic syndromes. *Nat.Rev.Neurol.*, 9, 86-97.
- Bekinschtein, P., Cammarota, M., Igaz, L. M., Bevilaqua, L. R., Izquierdo, I., & Medina, J. H. (2007). Persistence of long-term memory storage requires a late protein synthesis- and. *Neuron*, 53, 261-277.
- Butler, C. R., Graham, K. S., Hodges, J. R., Kapur, N., Wardlaw, J. M., & Zeman, A. Z. (2007). The syndrome of transient epileptic amnesia. *Ann.Neurol.*, 61, 587-598.
- Butler, C., van, E. W., Bhaduri, A., Hammers, A., Heckemann, R., & Zeman, A. (2013). Magnetic resonance volumetry reveals focal brain atrophy in transient epileptic amnesia. *Epilepsy Behav.*, 28, 363-369.
- Crawford, J. R. & Garthwaite, P. H. (2002). Investigation of the single case in neuropsychology: confidence limits on the abnormality of test scores and test score differences. *Neuropsychologia*, 40, 1196-1208.
- Crawford, J. R. & Garthwaite, P. H. (2005). Testing for suspected impairments and dissociations in single-case studies in neuropsychology: evaluation of alternatives using monte carlo simulations and revised tests for dissociations. *Neuropsychology.*, 19, 318-331.

- Cullen, P. K., Dulka, B. N., Ortiz, S., Riccio, D. C., & Jasnow, A. M. (2014). GABA-mediated presynaptic inhibition is required for precision of long-term memory. *Learn.Mem.*, *21*, 180-184.
- Davies, C., Starkey, S., Pozza, M., & Collingridge, G. (1991). GABA_B autoreceptors regulate the induction of LTP. *Nature*, *349*, 609-611.
- Dewar, M., Hoefeijzers, S., Zeman A, Butler C, & Della Sala, S. (2014). Impaired picture recognition in Transient Epileptic Amnesia. *Epilepsy and behaviour*, *42*, 107-116.
- Elliott, G., Isaac, C. L., & Muhlert, N. (2014). Measuring forgetting: a critical review of accelerated long-term forgetting studies. *Cortex*, *54*, 16-32.
- Evans JJ, Graham KS, Pratt KH, & Hodges JR (2003). The impact of disrupted cortico-cortico connectivity: a long-term follow up of a case of focal retrograde amnesia. *Cortex*, *39*, 767-790.
- Evans JJ, Breen EK, Antoun N, & Hodges JR (1996). Focal retrograde amnesia for autobiographical events following cerebral vasculitis: a connectionist account. *Neurocase*, 1-11.
- Furtinger, S., Pirker, S., Czech, T., Baumgartner, C., & Sperk, G. (2003). Increased expression of gamma-aminobutyric acid type B receptors in the hippocampus of patients with temporal lobe epilepsy. *Neurosci.Lett.*, *352*, 141-145.
- Gassmann, M. & Bettler, B. (2012). Regulation of neuronal GABA(B) receptor functions by subunit composition. *Nat.Rev.Neurosci.*, *13*, 380-394.

Giachino, C., Barz, M., Tchorz, J. S., Tome, M., Gassmann, M., Bischofberger, J. et al. (2014). GABA suppresses neurogenesis in the adult hippocampus through GABAB receptors. *Development*, *141*, 83-90.

Grande, L. A., Loeser, J. D., & Samii, A. (2008). Recurrent transient global amnesia with intrathecal baclofen. *Anesth.Analg.*, *106*, 1284-7.

Han, H., Cortez, M., & Snead O C (2012). GABAB receptor and absence epilepsy. In Noebels JL, M. Avoli, M. Rogawski, R. Olsen, & A. Delgado-Escueta (Eds.), *Jasper's Basic Mechanisms of the Epilepsies* (Fourth ed., pp. 242-256). Oxford University Press USA.

Hoefeijzers, S., Dewar, M., Della, S. S., Butler, C., & Zeman, A. (2015). Accelerated Long-Term Forgetting Can Become Apparent Within 3-8 Hours of Wakefulness in Patients With Transient Epileptic Amnesia. *Neuropsychology*, *29*, 117-126.

Hollnagel, J. O., Maslarova, A., Haq, R. U., & Heinemann, U. (2014). GABAB receptor dependent modulation of sharp wave-ripple complexes in the rat hippocampus in vitro. *Neurosci.Lett.*, *574*, 15-20.

Hornberger, M., Mohamed, A., Miller, L., Watson, J., Thayer, Z., & Hodges, J. R. (2010). Focal retrograde amnesia: Extending the clinical syndrome of transient epileptic amnesia. *J.Clin.Neurosci.*, *17*, 1319-1321.

Hosford, D. A., Clark, S., Cao, Z., Wilson, W. A., Jr., Lin, F. H., Morrisett, R. A. et al. (1992). The role of GABAB receptor activation in absence seizures of lethargic (lh/lh) mice. *Science*, 257, 398-401.

Hsieh, J. C. & Penn, R. D. (2006). Intrathecal baclofen in the treatment of adult spasticity. *Neurosurg.Focus.*, 21, e5.

Jansari, A. S., Davis, K., McGibbon, T., Firminger, S., & Kapur, N. (2010). When "long-term memory" no longer means "forever": analysis of accelerated long-term forgetting in a patient with temporal lobe epilepsy. *Neuropsychologia*, 48, 1707-1715.

Khundakar, A. A. & Zetterstrom, T. S. (2011). Effects of GABAB ligands alone and in combination with paroxetine on hippocampal BDNF gene expression. *Eur.J.Pharmacol.*, 671, 33-38.

Kofler, M., Kronenberg, M. F., Rifici, C., Saltuari, L., & Bauer, G. (1994). Epileptic seizures associated with intrathecal baclofen application. *Neurology*, 44, 25-27.

Kopelman MD (2004). Focal retrograde amnesia and the attribution of causality: an exceptionally critical review. *Cognitive Neuropsychology*, 17, 585-621.

Lancaster, E., Lai, M., Peng, X., Hughes, E., Constantinescu, R., Raizer, J. et al. (2010). Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. *Lancet Neurol.*, 9, 67-76.

Levine B, Black SE, Cabeza R, Sinden M, McIntosh AR, Toth JP et al. (1998). Episodic memory and the self in a case of isolated retrograde amnesia. *Brain*, *121*, 1951-1973.

Levine, B., Svoboda, E., Hay, J. F., Winocur, G., & Moscovitch, M. (2002). Aging and autobiographical memory: dissociating episodic from semantic retrieval. *Psychol.Aging*, *17*, 677-689.

Levine, B., Svoboda, E., Turner, G. R., Mandic, M., & Mackey, A. (2009). Behavioral and functional neuroanatomical correlates of anterograde autobiographical memory in isolated retrograde amnesic patient M.L. *Neuropsychologia*, *47*, 2188-2196.

Markowitsch, H. J. & Staniloiu, A. (2013). The impairment of recollection in functional amnesic states. *Cortex*, *49*, 1494-1510.

Midorikawa, A. & Kawamura, M. (2007). Recovery of long-term anterograde amnesia, but not retrograde amnesia, after initiation of an anti-epileptic drug in a case of transient epileptic amnesia. *Neurocase.*, *13*, 385-389.

Milton, F., Muhlert, N., Pindus, D. M., Butler, C. R., Kapur, N., Graham, K. S. et al. (2010). Remote memory deficits in transient epileptic amnesia. *Brain*, *133*, 1368-1379.

Moor, E., DeBoer, P., & Westerink, B. H. (1998). GABA receptors and benzodiazepine binding sites modulate hippocampal acetylcholine release in vivo. *Eur.J.Pharmacol.*, *359*, 119-126.

Munoz, A., Arellano, J. I., & DeFelipe, J. (2002). GABABR1 receptor protein expression in human mesial temporal cortex: changes in temporal lobe epilepsy. *J.Comp Neurol.*, 449, 166-179.

Nugent, S., Katz, M. D., & Little, T. E. (1986). baclofen overdose with cardiac conduction abnormalities: case report and review of the literature. *J.Toxicol.Clin.Toxicol.*, 24, 321-328.

O'Connor, M., Sieggreen, M. A., Ahern, G., Schomer, D., & Mesulam, M. (1997). Accelerated forgetting in association with temporal lobe epilepsy and paraneoplastic encephalitis. *Brain Cogn*, 35, 71-84.

Osten, P., Wisden, W., & Sprengel, R. (2007). Molecular Mechanisms of synaptic function in the hippocampus. In P.Andersen, R. Morris, D. Amaral, T. Bliss, & J. O'Keefe (Eds.), *The Hippocampus Book* (pp. 243-295).

Palombo, D. J., Alain, C., Soderlund, H., Khuu, W., & Levine, B. (2015). Severely deficient autobiographical memory (SDAM) in healthy adults: A new mnemonic syndrome. *Neuropsychologia*, 72, 105-118.

Rosenblum, D. & Desan, P. (2014). Transient Global Amnesia from Intrathecal baclofen: a case report. *P M & R* 6[9], S308.

Rubin, D. C. & Greenberg, D. L. (1998). Visual memory-deficit amnesia: a distinct amnesic presentation and etiology. *Proc.Natl.Acad.Sci.U.S.A*, 95, 5413-5416.

Saltuari, L., Marosi, M. J., Kofler, M., & Bauer, G. (1992). Status epilepticus complicating intrathecal baclofen overdose. *Lancet*, *339*, 373-374.

Sandyk, R. & Gillman, M. A. (1985). baclofen-induced memory impairment. *Clin.Neuropharmacol.*, *8*, 294-295.

Staniloiu, A. & Markowitsch H (2014). Dissociative Amnesia. *Lancet Psychiatry*, *1*, 126-141.

Svoboda, E., McKinnon, M. C., & Levine, B. (2006). The functional neuroanatomy of autobiographical memory: A meta-analysis. *Neuropsychologia*, *44*, 2189-2208.

Terunuma, M., Revilla-Sanchez, R., Quadros, I. M., Deng, Q., Deeb, T. Z., Lumb, M. et al. (2014). Postsynaptic GABAB receptor activity regulates excitatory neuronal architecture and spatial memory. *J.Neurosci.*, *34*, 804-816.

Tramoni, E., Felician, O., Barbeau, E. J., Guedj, E., Guye, M., Bartolomei, F. et al. (2011). Long-term consolidation of declarative memory: insight from temporal lobe epilepsy. *Brain*, *134*, 816-831.

Tu, S., Miller, L., Piguet, O., & Hornberger, M. (2014). Accelerated forgetting of contextual details due to focal medio-dorsal thalamic lesion. *Front Behav.Neurosci.*, *8*, 320.

Turi, G. F., Wittmann, G., Lechan, R. M., & Losonczy, A. (2015). Ambient GABA modulates septo-hippocampal inhibitory terminals via presynaptic GABA_B receptors. *Neuropharmacology*, 88, 55-62.

White, J. H., McIlhinney, R. A., Wise, A., Ciruela, F., Chan, W. Y., Emson, P. C. et al. (2000). The GABA_B receptor interacts directly with the related transcription factors CREB2 and ATFx. *Proc.Natl.Acad.Sci.U.S.A*, 97, 13967-13972.

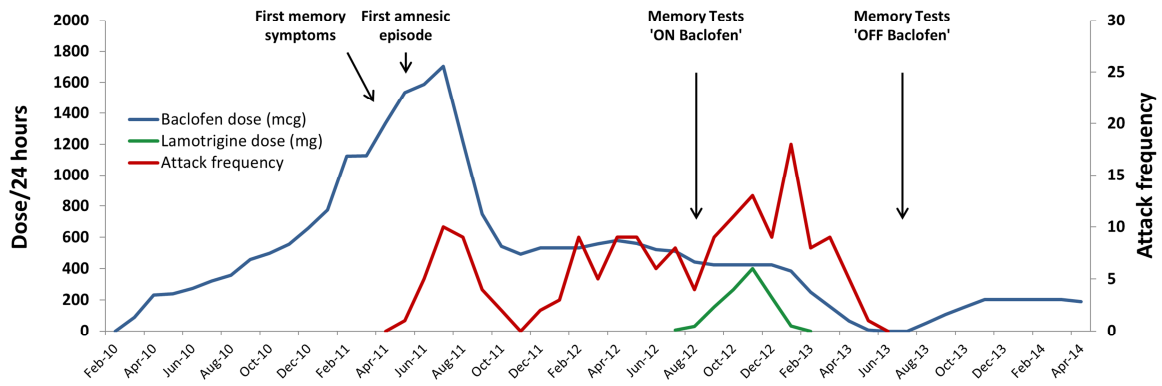
Zeman, A. & Butler, C. (2010). Transient epileptic amnesia. *Curr.Opin.Neurol.*, 23, 610-616.

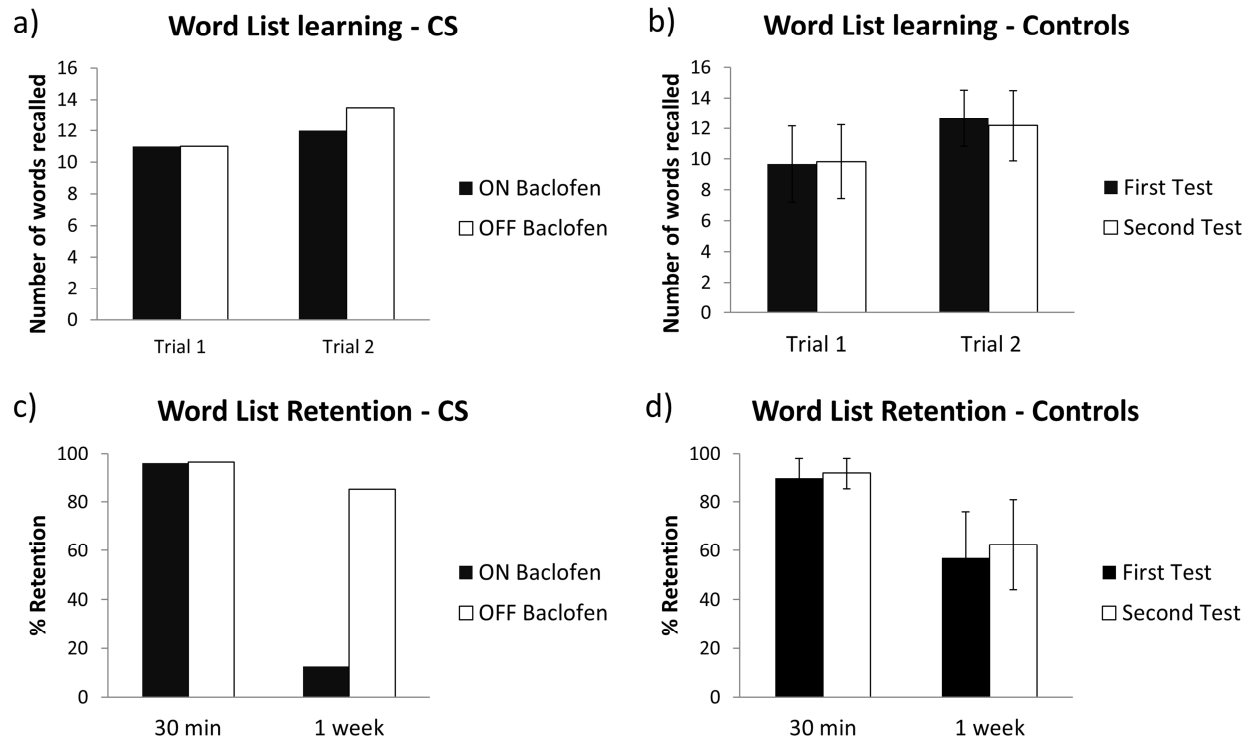
Zeman, A., Butler, C., Muhlert, N., & Milton, F. (2013). Novel forms of forgetting in temporal lobe epilepsy. *Epilepsy Behav.*, 26, 335-342.

Table 1

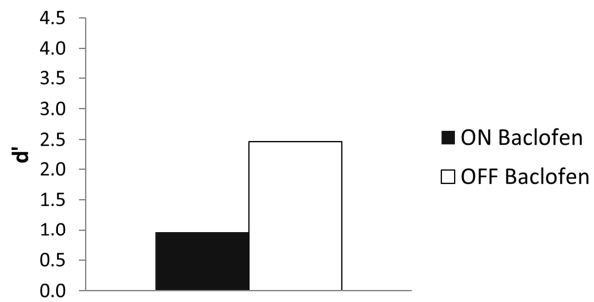
	TGA	TEA	TIA	Functional
Typical age	50+ years	50+ years	50+ years	Any age after early childhood, typically 3-4 th decades
Typical Duration	4-6 hours	<1 hour	Variable	days or months
Memory impairment during episode	Dense anterograde amnesia; variable retrograde amnesia	Variable mix of anterograde and retrograde amnesia – may later remember attack	Not well characterised	Variable, but often dense retrograde amnesia (+/- loss of personal identity) with preserved anterograde memory
Other features (sometimes present)	Headache, nausea	Olfactory hallucinations, automatisms, brief loss of awareness	Focal neurological symptoms and signs typically present, usually arising from posterior circulation	Other functional symptoms and signs may be present; mood disturbance
Precipitants	Physical (esp immersion in cold water) and	Waking	-	Stressful life events, minor head injury, mood disturbance

	psychological stresses			
Recurrence rate	6-10% patients/year	Around 1 seizure/month prior to treatment	Recognised but not well characterised	Can be isolated, recurrent or chronic
Past medical history	+/- migraine	No established risk factors	Cerebrovascular risk factors	Prior psychiatric illness, prior 'organic' transient amnesia, substance abuse
Interictal/postictal /post-episode memory	Subtle subclinical impairment may persist for days-months, but no permanent deficit	+/- mild impairment on standard tests; accelerated long-term forgetting, autobiographical memory loss	Risk of permanent memory impairment from completed stroke	Variable
Investigations	Hippocampal high signal lesions on DTI at 24-72 hours in most patients	Routine and sleep-deprived EEG may show epileptiform discharges	Neuroimaging may show evidence of old or new ischaemic change	Normal structural neuroimaging; functional imaging changes are described, especially right fronto-temporal

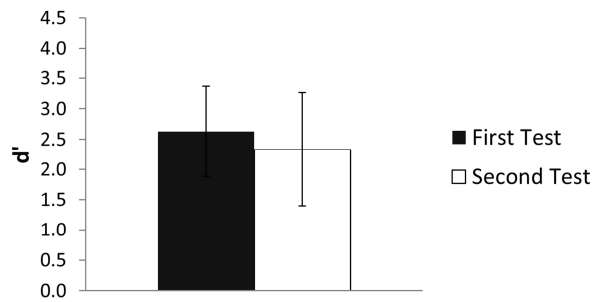




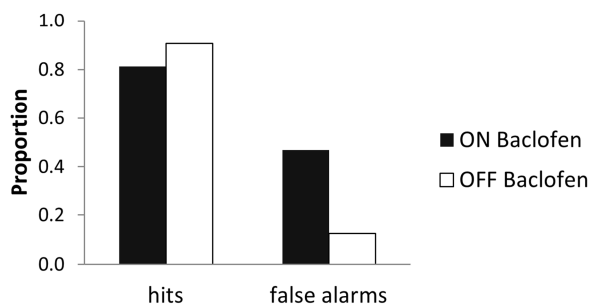
a) 1-week Word Recognition - CS



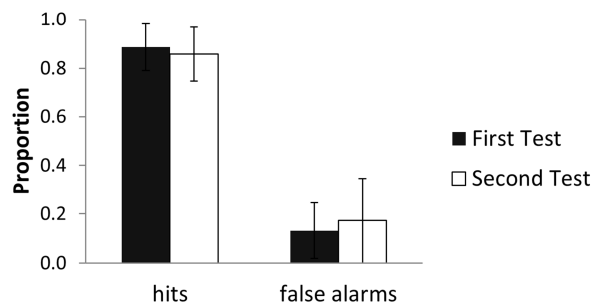
b) 1-week Word Recognition - Controls

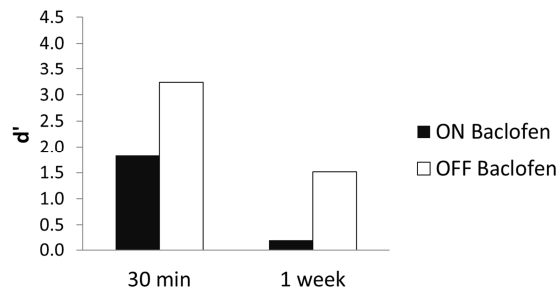
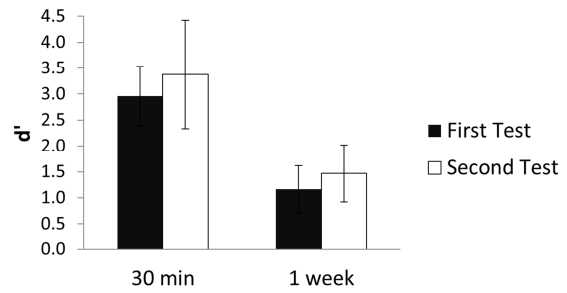


c)

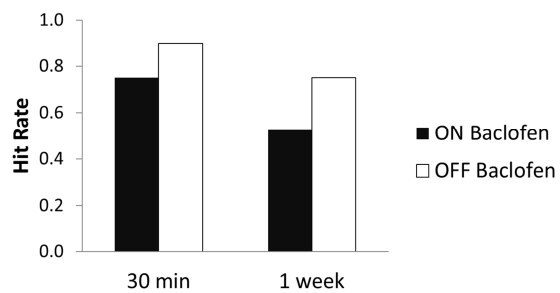


d)

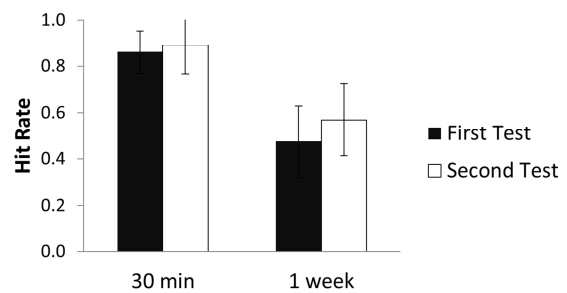


a) **Picture Recognition - CS**b) **Picture Recognition - Controls**

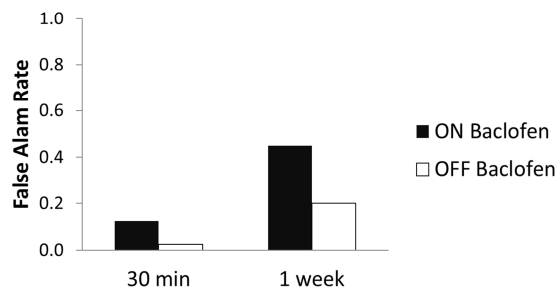
c)



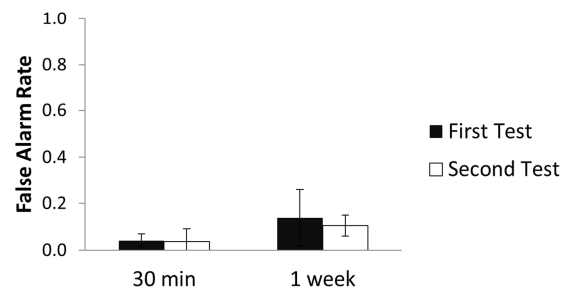
d)



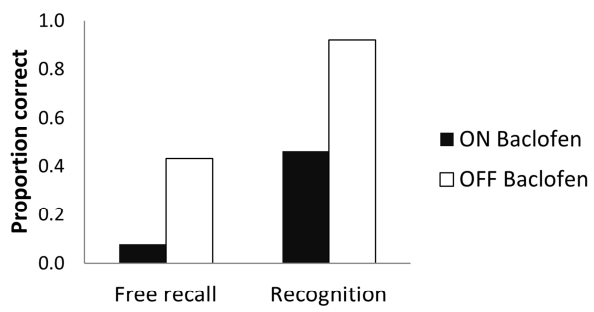
e)



f)



a) 1-week Incidental Story - CS



b) 1-week Incidental Story - Controls

