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Psychogenic Amnesia:

Syndromes, outcome, and patterns of retrograde amnesia.

Neil A. Harrison^{1,2}, Kate Johnston¹, Federica Corno¹, Sarah J. Casey^{1,3}, Kimberley Friedner¹, Kate Humphreys^{1,4}, Eli Joseph Jaldow¹, Mervi Pitkanen¹, Michael D. Kopelman^{1*}

¹ King's College London, Academic Neuropsychiatry, Psychological Medicine CAG, Institute of Psychiatry, Psychology, and Neuroscience, London, SE1 7EH.

² Brighton & Sussex Medical School, University of Sussex, Brighton BN1 9RR

³ Acquired Brain Injury Ireland, Dublin, Ireland

⁴ Royal Free London NHS Foundation Trust, Clinical Neuropsychology, London, NW3 2QG

***Corresponding author address:**

Professor M.D. Kopelman, Academic Neuropsychiatry, 3rd Floor Adamson Centre, South Wing, St. Thomas's Hospital, London, SE1 7EH, UK.

Tel: +44 20 7188 0207

Email: michael.kopelman@kcl.ac.uk

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Abstract

There are very few case series of patients with acute psychogenic memory loss (also known as dissociative/functional amnesia), and still fewer studies of outcome, or comparisons with neurological memory-disordered patients. Consequently, the literature on psychogenic amnesia is somewhat fragmented and offers little of prognostic value for individual patients. In the present study, we reviewed the case records and neuropsychological findings in 53 psychogenic amnesia cases (3M:1F), in comparison with 21 consecutively recruited neurological memory-disordered patients and 14 healthy controls. In particular, we examined the pattern of retrograde amnesia on an assessment of autobiographical memory (the Autobiographical Memory Interview). We found that our patients with psychogenic memory loss fell into four distinct groups, which we categorised as: (i) fugue state, (ii) fugue-to-focal retrograde amnesia, (iii) psychogenic focal retrograde amnesia following a minor neurological episode, and (iv) patients with gaps in their memories. While neurological cases were characterised by relevant neurological symptoms, a history of a past head injury was actually more common in our psychogenic cases ($p=0.012$), perhaps reflecting a 'learning episode' predisposing to later psychological amnesia. As anticipated, loss of the sense of personal identity was confined to the psychogenic group. However, clinical depression, family/relationship problems, financial/employment problems, and failure to recognise the family were also statistically more common in that group. The pattern of autobiographical memory loss differed between the psychogenic groups: fugue cases showed a severe and uniform loss of memories for both facts and events across all time-periods, whereas the two focal retrograde amnesia groups showed a 'reversed' temporal gradient with relative sparing of recent memories. After 3-6 months, the fugue patients had improved to normal scores for facts and near-normal scores for events. By contrast, the two focal retrograde amnesia groups showed a lesser improvement and continued to show a reversed temporal gradient. In conclusion, the outcome in psychogenic amnesia, particularly those characterised by fugue, is better than generally supposed.

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Findings are interpreted in terms of Markowitsch's and Kopelman's models of psychogenic amnesia, and with respect to Anderson's neuroimaging findings in memory inhibition.

Abbreviations:

AMI Autobiographical Memory Interview

BDI Beck Depression Inventory

DSM Diagnostic and Statistical Manual

FRA Focal Retrograde Amnesia

ICD International Classification of Diseases

NART-R National Adult Reading Test-Revised

PTSD Post-Traumatic Stress Disorder

SPECT Single photon emission computerised tomography

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1. Introduction

Psychogenic amnesia refers to cases of memory loss presumed to have a psychological, rather than neurological, cause; and is either 'global' or situation-specific (Kopelman, 1987, 2002). Global psychogenic amnesia is characterised by a sudden loss of autobiographical memories for the whole of a person's past. In psychogenic fugue, there is a loss of sense of personal identity and a period of wandering (psychogenic fugue), which lasts from a few days to about 4 weeks (Schacter *et al.*, 1982; Kopelman, 2002). In 'focal retrograde amnesia', the memory loss is much more persistent (Kapur, 1993; Kopelman, 2000; Serra *et al.*, 2007; Hennig-Fast *et al.*, 2008; Tramoni *et al.*, 2008). Situation-specific amnesia refers to a gap in memory for a traumatic incident and can arise in a variety of circumstances: for example, post-traumatic stress disorder (PTSD) (Brewin *et al.*, 2011) or being the victim of an offence (Mechanic *et al.*, 1998; Andrews *et al.*, 2000).

Three factors have been identified as predisposing factors for global psychogenic amnesia (Kopelman, 1987, 2002): (i) a severe precipitating stress, such as marital or emotional crisis, bereavement, a financial crisis or during wartime (Kanzer, 1939; Sargant and Slater, 1941); (ii) a history of depressed mood and suicidal ideas (Stengel, 1941; Berrington *et al.*, 1956); and (iii) a previous history of a transient, neurological amnesia (Stengel, 1941; Berrington *et al.*, 1956; Thomas-Anterion *et al.*, 2008; Fujiwara *et al.*, 2008). Coons and Milstein (1992) also identified previous histories of childhood trauma, sexual abuse, and alcohol/ substance misuse problems. However, many previous descriptions of psychogenic amnesias consisted of case-reports, making it difficult to generalise about predisposing factors. In cases of focal retrograde amnesia (Kapur, 1993, 2000), psychogenic factors are often suspected (Kopelman, 2000) but may not initially be obvious.

The neuropsychological profile of the memory impairment reported in cases of global psychogenic amnesia is variable. While retrograde autobiographical memory is characteristically impaired, anterograde memory has been described as intact, mildly, or severely impaired (Gudjonsson *et al.*,

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1985; Barba *et al.*, 1997; Kopelman *et al.*, 1994; Serra *et al.*, 2007; Thomas *et al.*, 2008); Hennig-Fast *et al.*, 2008). The involvement of semantic memory is disputed: Schacter *et al.* (1982) reported that fugue is an example of an episodic/semantic dissociation, whereas others have reported involvement of both episodic and (personal) semantic memory (Kopelman *et al.*, 1994). Both 'reversed' and 'flat' temporal gradients have been reported. In general, the literature on recovery from psychogenic amnesia remains sparse: the prognosis for recovery from global psychogenic amnesia has sometimes been reported as good (Parfitt and Gall, 1944), but in many cases the amnesia persists (Serra *et al.*, 2007; Kapur, 2000; Hennig-Fast *et al.*, 2008). When resolution occurs, it is sometimes prompted by chance cues in the environment (Schacter *et al.*, 1982), but may depend on a variety of factors (McKay and Kopelman, 2009). However, these observations have again been based on individual case-reports or very small case series with very few follow-up studies.

Varying patterns of abnormality have been reported in functional imaging studies, including both prefrontal activation and inhibition (Markowitsch *et al.*, 1997; Glisky *et al.*, 2004; Piolino *et al.*, 2005; Hennig-Fast *et al.*, 2008; Brand *et al.*, 2009; Kikuchi *et al.*, 2009), temporal lobe changes (Yasuno *et al.*, 2000; Sellal *et al.*, 2002; Thomas-Artérion *et al.*, 2008), posterior cortical changes (Botzung *et al.*, 2008; Arzy *et al.*, 2011), or a combination of such findings (Magnin *et al.*, 2014; for review, see Staniloiu and Markowitsch, 2014). This variability may reflect differences in the syndromes described, the time-delays until imaging was conducted, and the imaging methods employed.

There is a dearth of large studies of psychogenic amnesia, follow-up investigations, or comparisons between different types of psychogenic amnesia. In the present investigation, we examined a series of 53 cases of psychogenic amnesia with the following aims:

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- (i) To describe different syndromes in psychogenic amnesia (including fugue, psychogenic focal retrograde amnesia, and memory ‘gaps’), assessed during and/or after the amnesic episode;
- (ii) To explore their association with clinical and psychosocial factors, and to compare these with healthy controls and a neurological comparison group;
- (iii) To examine the neuropsychological profiles in psychogenic cases, including performance on anterograde memory tests;
- (iv) To describe patterns of performance on an autobiographical memory task, and how these patterns changed through time;
- (v) To compare psychogenic cases with the neurological and healthy controls on the autobiographical memory task.

2. Materials and methods

2.1. Participants

We report findings in 53 cases of psychogenic amnesia seen as in- or outpatients at St. Thomas’s Hospital, London, between 1990 and 2008. All were diagnosed with syndromes of psychogenic amnesia, as described below, consistent with ICD or DSM definitions of dissociative amnesia (ICD-10, F44.0; DSM-5, 300.12), dissociative fugue (ICD-10, F44.1), or dissociative amnesia with dissociative fugue (DSM-5, 300.13). Cases were excluded if amnesia was directly attributable to neurological disease, alcohol, or substance misuse.

Twenty-one patients with neurological memory disorders were included for comparison, drawn from consecutive referrals to the St Thomas’s Neuropsychiatry and Memory Disorders Clinic (Johnston, 2006). 11 were memory-disordered patients of various aetiologies (for example, cerebral hypoxia, herpes simplex encephalitis); 10 had early stage Alzheimer’s disease according to NINDS-ADRDA criteria (McKhann *et al.*, 1984, 2011).

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Fourteen healthy volunteers without a history of memory problems were recruited from the local community to serve as a healthy control group. Exclusion criteria for healthy controls were any history of significant neurological or psychiatric disorder, including alcohol/substance misuse (Johnston, 2006).

2.2 *Clinical records*

Medical records from the psychogenic and neurological groups were reviewed for clinical history, psychosocial factors, and neuropsychological test scores. Handwritten clinical notes, clinical correspondence, discharge summaries, follow-up reports, neuroimaging (CT, MRI, and PET), electrophysiology (EEG), and laboratory findings were reviewed. Controls were administered a standardised background questionnaire asking about clinical and psychosocial factors (Johnston, 2006).

For each psychogenic patient we recorded:

- (i) The length of the ‘original’ gap in memory, i.e. at the time of the initial episode.
- (ii) The duration of the ‘residual’ amnesic gap (i.e. at inpatient hospital discharge or first outpatient visit).
- (iii) The time between the onset of the amnesic episode and when the patient was first seen by our (inpatient or outpatient) clinical team.

2.3 *Background neuropsychological assessment*

Because patients were seen clinically over the course of 18 years, varying tests had been employed. However, in virtually all cases, the National Adult Reading Test - Revised (NART-R; Nelson and Willison, 1991) was used to estimate premorbid intellectual ability and, most commonly, the FAS verbal fluency test (Benton and Hamsher, 1976) as a brief measure of executive function.

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2.4 *Anterograde Memory*

The Wechsler Memory Scale, revised edition (Wechsler, 1987), the Doors and People test (Baddeley *et al.*, 1994), and/or the Recognition Memory Test (Warrington, 1984) had been employed to assess verbal and visual recall and recognition memory.

2.5 *Retrograde Memory*

Retrograde memory was assessed using the Autobiographical Memory Interview (AMI; Kopelman *et al.*, 1989, 1990), a semi-structured interview asking about (personal semantic) facts and autobiographical episodes (incidents) across three broad time-bands from a person's past life: childhood, early adult life, and recent.

2.6 *Psychosocial Factors*

Psychological and psychosocial factors were identified from the clinical records (see Supplementary Material). Participants also rated current symptoms of depression on the Beck Depression Inventory (BDI-II; Beck and Steer, 1987).

2.7 *Follow-up of Amnesia*

If patients were considered to be 'in' a fugue episode, or were seen within 3 months of the onset of a 'focal retrograde' amnesia, they were classified as being assessed 'during' their amnesia. Follow-up assessment was conducted after the fugue had ended, or 6 months after onset in focal retrograde cases.

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2.8 *Statistical Analyses*

In order to compare performance on cognitive functions where differing tests had been employed, z-scores were calculated in terms of either published norms or control values (where norms were not available). These were then converted to indices with a mean of 100 and a standard deviation of 15.

All data were recorded and analysed using SPSS 20. One-way ANOVAs with Sidak post-hoc tests were used to compare the four subgroups of psychogenic patients with healthy controls and/or neurological patients. Performance on the Autobiographical Memory Interview (AMI) was analysed using mixed-model 2-way ANOVAs with Sidak-adjusted pairwise comparisons.

3. Results

Fifty-three patients with psychogenic amnesia were recruited and assigned to four groups on the basis of their history and pattern of amnesia (see Table 1).

TABLE 1 APPROX HERE

3.1.1 *Fugue State*

Patients were diagnosed with ‘fugue’ if, at the time of diagnosis, they had reported an abrupt loss of autobiographical memory and either the sense of personal identity and/or a period of wandering, and there was resolution within 4 weeks (often a few hours or days). Fourteen out of 16 cases had documented loss of personal identity. The remaining two patients had documented episodes of wandering, and then they emerged from the episode wondering where they were and amnesic for how they had got there. One of these cases had travelled from south-east London to Glasgow, a distance of over 400 miles, during the course of 7 hours, which he could not recall at all. Neurological causation was excluded. During the fugue, the ‘initial’ amnesia usually covered the whole of a person’s life but, after recovery, the patients reported that there was a *residual* amnesic

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gap covering only the period of the fugue. The (unusually) high rate of ‘fugue’ cases in this series reflected local conditions: fugue patients had often been picked up by the police in central London parks and railway termini (having travelled from elsewhere), and they were then taken to the St Thomas’s Emergency department.

Case 1: Fugue

A 26-year-old man was reported missing. He was found by police 6 days later wandering around a central London park. He reported that he did not know where he was, why he was there, or what he was doing. The police found an address in his bag and took him home where he did not recognise his family. He was admitted to St Thomas’s Hospital. Six days later, when given an interview under sedation, he recalled his autobiographical memories, including a few that occurred during the ‘missing’ period. He recalled a happy childhood, marred by bereavement, passing his school exams, working 6 years at a department store, and the break-up of an engagement. Although there was no previous psychiatric contact, he had become depressed before the onset of his fugue: he described anxiety about finances, falling behind in rental payments, and caring for a sick mother. His account of his fugue was: “I had a breakdown. My brain decided to close down. I felt as if placed into a grown-up body without knowing the history of the body.”

3.1.2 *Fugue-to-Focal Retrograde Amnesia (Fugue-to-FRA)*

In some cases, a prolonged focal retrograde amnesia followed a more typical fugue episode. We will refer to these cases as ‘Fugue-to-FRA’, in which an initial fugue-like episode (with a period of wandering and usually loss of personal identity) was followed by ‘relearning’ of personal identity and apparently *normal* anterograde memory, but *persistent* (pre-onset) retrograde amnesia. These patients reported that their residual retrograde amnesia covered at least 6 months, and sometimes the entirety of their lives.

Case 2: Fugue-to-Focal Retrograde Amnesia

B was a 28-year-old man whose amnesia commenced 10 years earlier. He had gone missing after training with the Territorial Army. He described awakening in a copse of trees, then

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walking 20 miles, finding himself eventually at a seaside resort. He recalled begging for money to obtain food and sleeping in a cemetery. When noticed by the police, he was outside a bank, unable to give them any personal information. Following admission to a psychiatric hospital, a Missing Person's report was made. Five months later, his parents visited him in hospital, but he did not recognise them, saying that they were "unfamiliar". He said that he could not remember anything from his previous life until he "awakened" in the woods. However, he had taken a lot of money out of his bank account before going missing, and his parents had separated shortly before his disappearance. B said that he was "not too concerned" to get his memories back, because he was worried what he might find. The family reported that there had not been any previous psychiatric history.

3.1.3 *Focal Retrograde Amnesia (FRA)*

In these cases, there was severe retrograde amnesia, and only minimal or no anterograde impairment. There was no period of wandering. Onset was generally abrupt, often following a minor neurological event or head injury, insufficient to account for the severity of the retrograde memory loss. Unlike fugue, the amnesia did not resolve within 4 weeks; in some cases, there was an initial loss of personal identity, but it was transient, the patients stating that they had "re-learned" their identity. Three of these cases reported that they eventually recovered most of their memories with a residual amnesic gap of 2 years or less for the period immediately pre-onset; in the remaining cases, significant amnesia persisted.

Case 3: Focal Retrograde Amnesia

C was a 55-year-old man, who collapsed at work with a transient left-sided weakness and complete loss of autobiographical memory. At initial admission, he was disorientated in time, place, and person with a mild loss of power in the left arm and leg and an equivocally up-going left plantar. An MRI scan showed only very minor small vessel disease bilaterally, consistent with previously diagnosed hypercholesterolemia and diabetes. However, the attending physicians were confident that his autobiographical memory loss was entirely disproportionate to his neurological signs, which rapidly resolved. At first, he did not recognise his wife, and could not remember the names or ages of his wife and children. After only a few days, he said that he had "re-learned" his personal identity, also stating that: "Each

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day I remember more of the day before.” Formal tests confirmed a severe and extensive retrograde amnesia with intact anterograde memory. Although initially angry at any suggestion that there might be a psychological component to his memory loss, a history of emotional disturbance eventually emerged. He became more willing to accept a psychological explanation and, following an interview under sedation, C. recovered most of his memories, apart from the two years immediately before the onset.

3.1.4 Gaps in memory

‘Gaps in memory’ were defined as periods of discrete memory loss, associated with enhanced stress, as in PTSD, ranging from hours to several weeks. We excluded anyone charged with an offence. Some cases reported multiple amnesic gaps: two patients had a single gap, 3 reported 2 to 5 memory gaps. One case had reported transient loss of personal identity, but none reported episodes of wandering, or loss of all earlier memories, as in fugue. This group differed from the FRA group because they reported memory loss for a particular incident or incidents, but not for more prolonged periods of their lives. Patients reported either short memory gaps lasting ≤ 6 hours or more prolonged amnesic gaps, lasting up to 90 days. In all these cases, an informant was available and interviewed, and a standard EEG was performed. Cases of possible transient epileptic amnesia were excluded from this subgroup.

Case 4: Gaps in Memory

F described ‘gaps’ in his memory, which appeared unrelated to the affective content of what he had forgotten, and did not respond to cueing. There was a history of clinical depression, initially resulting from severe work stresses, and treated with various antidepressants. He had been unemployed for the last 8 years, and he remained stressed and intermittently depressed. There was no evidence of epilepsy. His scores on standard tests of anterograde memory were generally excellent.

3.2.1 Demographic variables

Table 1 shows mean gender ratios and age across groups. For gender ratio, the psychogenic amnesia groups did not differ significantly from one another or from the controls or neurological patients

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($p > 0.05$), although cases of psychogenic amnesia were approximately three times more common in men than women overall (χ^2 (df 1)=11.79, $p=0.001$). With respect to age, a one-way ANOVA across all groups gave a significant main effect of age, $F_{(5,82)}=4.31$, $p=0.002$, $\eta^2_p=0.21$; on post-hoc Sidak tests, the neurological group differed significantly from the two FRA groups ($p=0.003$, $p=0.046$), but not from fugue ($p=0.57$), Gaps ($p=0.86$) or controls ($p=0.99$). Controls differed from the Fugue-to-FRA group only ($p=0.025$).

3.2.2 Scores on affective rating scale (BDI-II)

Table 1 also shows scores on the Beck Depression Inventory. The mean of each psychogenic group was more than 2 standard deviations higher than the controls'. The Fugue-to-FRA and Gaps groups fell in the 'moderate', the Fugue and FRA groups in the 'mild', and the neurological patients within the 'minimal' severity range. One-way ANOVA confirmed a significant between-group difference ($F_{(5,82)}=5.52$, $p=0.001$, $\eta^2_p=0.32$) with post-hoc tests showing significantly higher depression scores in the Fugue-to-FRA ($p=0.001$) and 'gaps' groups ($p=0.03$) compared with controls. The neurology group differed significantly from the Fugue-to-FRA group ($p=0.03$), but not from the controls ($p=0.66$)

3.2.3 Clinical features of the amnesia.

Figure 1a shows the frequency of key clinical features of the amnesia in the psychogenic and control groups, as recorded in the clinical records. Loss of personal identity had been recorded in 14 out of 16 cases of Fugue (see above). An initial, transient loss of personal identity also occurred commonly in the two FRA groups (81.3%, 62.5%), but was much less common in the Gaps group (20%) (χ^2 (2)=6.34, $p=0.042$, $\phi_c=0.40$). Failure to recognise the family was more common in the two FRA groups than the fugue and 'gaps' groups (Figure 1a: χ^2 (3)=10.78, $p=0.013$, $\phi_c=0.45$).

3.2.4 Background clinical and psychosocial factors

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Figure 1b shows frequencies of background clinical and psychosocial factors. A history of somatisation or PTSD was not as common as expected, but was most frequent in the FRA and memory ‘gaps’ groups. χ^2 tests indicated that psychogenic patients showed significantly higher rates than controls in reporting a neurological history ($\chi^2(4)=12.57, p=0.013, \phi_c=0.43$), head injury ($\chi^2(4)=15.37, p=0.003, \phi_c=0.48$), past or recent depression ($\chi^2(4)=21.01, p<0.001, \phi_c=0.58$), relationship or family difficulties ($\chi^2(4)=13.85, p=0.008, \phi_c=0.46$), and financial or employment problems ($\chi^2(4)=16.02, p=0.003, \phi_c=0.49$).

FIGURE 1 APPROX HERE

3.2.5 Psychogenic versus neurological groups.

Figure 2 compares the combined psychogenic group and the neurological comparison group on clinical and background factors. Interestingly, head injury was more common in the psychogenic group than the neurological (41.5% versus 10.0%: $\chi^2(1)=6.53, p=0.012, \phi_c=0.30$). Table 2a indicates the relative risks attributed to these variables: loss of personal identity, a past or recent history of depression, family or relationship problems, and financial or employment problems were most predictive of psychogenic amnesia. A binary logistical regression with stepwise forward entering of the variables showed that a history of neurological symptoms, loss of personal identity, a history of financial or employment problems, and a history of somatisation disorder, correctly classified 98.5% of patients ($\chi^2(df 4)=78.03, p<0.001$).

FIGURE 2 AND TABLE 2 APPROX HERE

3.2.6 Background neuropsychological tests

Table 3a shows means scores for NART-R (estimated premorbid IQ) and FAS verbal fluency. One-way ANOVAs indicated no significant difference between groups for NART-R ($F_{(5,62)}=0.74$,

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$p=0.60$, $\eta^2_p=0.06$), but a significant difference for FAS ($F_{(5,51)}=4.75$, $p=0.001$, $\eta^2_p=0.32$). On post-hoc tests, corrected for multiple comparisons ($\alpha=0.01$), healthy controls only performed significantly better than the neurological group ($p=0.001$).

TABLE 3 HERE

3.3 Scores on anterograde memory tests

Table 3a shows mean scores on verbal and visual recall and recognition memory for each psychogenic subgroup (during the amnesic episode), neurological patients, and controls. Separate one-way ANOVAs showed a significant difference only on visual recall memory ($F_{(5,82)}=5.22$, $p=0.001$, $\eta^2_p=0.15$), attributable on post-hoc tests to the difference between controls and neurology patients ($p<0.001$).

Table 3b shows anterograde memory index scores for 38 patients tested ‘during’ the acute amnesic episode, and for 20 patients tested after the acute episode; scores are collapsed across the psychogenic groups. Across each memory domain (verbal and visual, recall and recognition) scores were higher in the follow-up phase than during the acute amnesic episode. For the 13 patients who were tested both ‘during’ and ‘after’ the amnesic episode, verbal recall scores were significantly higher at follow-up than during the acute episode (paired $t_{(11)}=3.65$, $p=0.004$, $d=0.91$). However, the differences for the other domains did not reach statistical significance ($t=0.76$ to 1.80 , $d=0.36$ to 0.75). For the remaining participants, tested during or after the acute episode, verbal recall memory was again significantly higher for patients tested at follow-up compared with those tested during the acute episode (independent $t_{(25)}=2.25$, $p=0.034$, $d=0.90$) with no significant differences across the other measures ($t=0.11$ to 1.27 , $d=0.04$ to 0.51).

3.4 Scores on autobiographical memory tests

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AMI data were available for 28 patients during their psychogenic amnesia episode and 19 patients at follow-up. Ten patients with psychogenic amnesia were assessed both ‘during’ and ‘after’ the acute amnesic phase, 18 only ‘during’ the amnesic episode, and 9 were first seen after the acute episode. Data were available for only one patient with memory ‘gaps’, who was excluded from these analyses.

3.4.1 Personal semantic facts

Figure 3a shows that Fugue patients performed poorly across all time-periods (childhood, young adulthood, recent) ‘during’ the amnesic episode, producing a ‘flat’ temporal gradient, contrary to theories of preserved semantic memory and an episodic/semantic dissociation in fugue (Schacter *et al.*, 1982). By contrast, the two FRA groups showed a ‘reversed temporal gradient’, performing much better for recent than earlier memories. A mixed model ANOVA gave a significant main effect of group ($F_{(3,37)}=16.11$, $p<0.001$, $\eta^2_p=0.81$) with Sidak-adjusted paired comparisons showing that the Fugue and both FRA groups were significantly impaired compared with controls (all $p<0.001$). There was also a significant group x time-period interaction ($F_{(6,74)}=3.70$, $p<0.01$, $\eta^2_p=0.23$), and further analysis of this interaction revealed that both Fugue-to-FRA ($F_{(2,36)}=15.66$, $p<0.001$; $\eta^2_p=0.47$) and FRA groups ($F_{(2,36)}=15.41$, $p<0.001$, $\eta^2_p=0.46$) showed significant time-period effects, consistent with reversed temporal gradients. There were no significant time-period effects in controls ($F_{(2,36)}=0.78$, $\eta^2_p=0.03$) or Fugue patients ($F_{(2,36)}=0.36$, $\eta^2_p=0.02$), consistent with the ‘flat’ gradients across time-period, observed in these groups.

FIGURE 3 HERE

Figure 3b indicates that the Fugue group showed the greatest improvement at follow-up, to the extent that their performance now matched that of the healthy controls. The two FRA groups also showed an overall improvement in scores, but continued to exhibit a reversed temporal gradient.

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ANOVA confirmed this significant main effect of group ($F_{(3,29)}=11.03, p<0.001, \eta^2_p=0.53$) with both the FRA ($p=0.001$) and Fugue-to-FRA ($p=0.005$), but not the Fugue, groups continuing to perform worse than controls on paired comparisons. A significant group x time-period interaction ($F_{(6,58)}=2.41, p=0.038, \eta^2_p=0.19$) was also observed, which reflected a significant time-period effect in the FRA group only ($F_{(2,28)}=10.02, p<0.001, \eta^2_p=0.42$), consistent with a reversed temporal gradient in this group. The Fugue-to-FRA and Fugue groups did not show significant time-period effects ($p=0.19, \eta^2_p=0.11; p=0.94, \eta^2_p=0.04$, respectively).

3.4.2. Autobiographical episodes

Figure 4a shows the recall of autobiographical episodes ‘during’ the amnesic episode. All psychogenic groups showed impaired performance across each of the time-periods (main effect of group: $F_{(3,37)}=32.75, p<0.001, \eta^2_p=0.73$; paired comparisons with controls all $p<0.001$). On visual inspection, the two FRA groups again showed a reversed temporal gradient, and the fugue group a relatively flat curve. This was confirmed by a highly significant group x time-period interaction ($F_{(6,74)}=8.88, p<0.001, \eta^2_p=0.42$), with both FRA groups showing significant time-period effects (Fugue-to-FRA, $F_{(2,36)}=35.00, p<0.001, \eta^2_p=0.66$; FRA, $F_{(2,36)}=27.72, p<0.001, \eta^2_p=0.61$), consistent with reversed temporal gradients. The Fugue group did not show a time-period effect ($p=0.49; \eta^2_p=0.05$), consistent with a ‘flat’ curve.

FIGURE 4 HERE

Figure 4b shows improved performance of all patient groups tested at follow-up compared with testing ‘during’ (Figure 4a) the amnesic episode. On visual inspection, the Fugue group tested at follow-up had improved to near-normal performance, although their scores still remained a little below the controls. The two FRA groups again showed reversed temporal gradients. Statistical analysis again showed a significant main effect of group ($F_{(3,29)}=5.70, p=0.003, \eta^2_p=0.37$), with both

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Fugue-to-FRA ($p=0.02$) and FRA groups ($p=0.03$), but not Fugue ($p=0.13$), showing significant impairment, compared with controls. There was a significant group x time-period interaction ($F_{(6,58)}=2.46$, $p=0.034$, $\eta^2_p=0.20$), attributable to a time-period effect in the Fugue-to-FRA group ($F_{(2,28)}=5.14$, $p=0.01$, $\eta^2_p=0.27$), but not the FRA ($p=0.18$, $\eta^2_p=0.12$) or Fugue ($p=0.37$, $\eta^2_p=0.07$) groups. In other words, at follow-up, only the Fugue-to-FRA showed a statistically significant reversed temporal gradient.

3.4.3 Subgroups tested on 2 (or more) occasions

Ten patients (7 of whom were from the two FRA groups) were tested on each of two occasions: ‘during’ amnesia and at follow-up. Because of the small sizes of the subgroups, these patients were merged into a single psychogenic group. On personal semantic memory, their scores improved significantly between the two testing occasions (during/follow-up) ($F_{(1,9)}=112.80$, $p<0.001$, $\eta^2_p=0.93$). However, the occasion by time-period interaction was not significant ($F_{(2,18)}=1.96$, $p=0.17$, $\eta^2_p=0.18$), indicating that the (‘reversed’) temporal gradient did not change through time. On autobiographical episodic memory, there was a significant improvement through time (main effect: $F_{(1,9)}=59.37$, $p<0.001$, $\eta^2_p=0.87$), but again no significant (occasion by time-period) interaction ($F_{(2,18)}=0.95$, $p=0.78$, $\eta^2_p=0.03$), indicating an unchanged slope of the gradient through time.

3.5.1 Comparison of psychogenic and neurological patients on autobiographical memory

Figure 5 compares the ‘combined’ psychogenic groups with neurological patients and healthy controls during amnesia and at follow-up.

FIGURE 5 APPROX HERE

3.5.2 Personal Semantic facts

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Figure 5a shows that, for personal semantic facts, the psychogenic group showed a reversed temporal gradient initially, with near-normal performance at follow-up, whereas neurological patients showed a conventional ('Ribot') temporal gradient. Comparing the psychogenic group 'during' amnesia with the two other groups revealed a significant main effect of group ($F_{(2,59)}=29.03, p<0.001, \eta^2_p=0.49$) with significant impairment in both the neurological ($p<0.01$) and psychogenic patients ($p<0.001$) compared with controls. The group x time-period interaction was also statistically significant ($F_{(4,118)}=12.07, p<0.001, \eta^2_p=0.29$), reflecting the contrasting temporal gradients of the two patient groups with the psychogenic group showing a significant time-period effect ($F_{(2,58)}=30.52, p<0.001, \eta^2_p=0.51$), whereas the neurological group did not ($F_{(2,58)}=1.15, p=0.325, \eta^2_p=0.04$). At follow-up, on comparing the psychogenic group with the neurological group, taken in isolation, there was a significant main effect of group ($F_{(1,37)}=13.65, p=0.001, \eta^2_p=0.27$), with the psychogenic group now scoring higher than the neurological group. There was also a significant group by time-period interaction ($F_{(2,74)}=3.21, p<0.05, \eta^2_p=0.08$), again reflecting the contrasting pattern of gradients in the neurological and psychogenic patients.

3.5.3 Autobiographical episodes

Figure 5b shows a similar pattern for recall of autobiographical episodes with the contrasting temporal gradients even more evident in the two patient groups. On comparing the psychogenic group 'during' amnesia with the other two groups, there was a significant main effect of group ($F_{(2,59)}=47.71, p<0.001, \eta^2_p=0.62$), with the two patient groups showing impairment relative to controls (both $p<0.001$), but not differing significantly from each other ($p=0.06$). A significant group x time-period interaction ($F_{(4,118)}=25.95, p<0.001, \eta^2_p=0.47$) reflected the differing temporal gradients of the psychogenic ($F_{(2,58)}=53.18, p<0.001, \eta^2_p=0.65$) and neurological ($F_{(2,58)}=9.32, p<0.001, \eta^2_p=0.24$) groups: 'reversed' versus Ribot gradients, respectively. At follow-up, the psychogenic group now performed significantly better than the neurological group (main effect:

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$F_{(1,37)}=24.97$, $p<0.001$, $\eta^2_p=0.40$). A significant group x time-period interaction ($F_{(2,74)}=8.39$, $p<0.001$ $\eta^2_p=0.18$) again indicated the contrasting slopes of the temporal gradients.

4. Discussion

From 53 patients with psychogenic (or ‘dissociative’) amnesia (approximately 3M:1F), we have distinguished four different clinical syndromes of psychogenic amnesia: (i) ‘fugue’, (ii) fugue-to-FRA; (iii) ‘pure’ FRA; and (iv) a group who reported a gap or gaps in memory from psychological causes. We have revealed important clinical and psychometric differences between these groups (particularly between the Fugue and FRA groups), including some that have prognostic value.

In psychogenic amnesia, loss of personal identity was most common in the two fugue groups (fugue, fugue-to-FRA), whereas failure to recognise family members was more common in the two FRA groups. A history of head injury or other neurological disorder, a clinical diagnosis of depression, family/relationship issues, or financial/employment problems were common across all the psychogenic groups, who generally scored within the ‘mild’/‘moderate’ range for depression on the Beck Inventory during the amnesia. Childhood problems, alcohol or substance misuse were fairly common across the different groups, but somatisation disorder and PTSD were less frequent than might have been anticipated; somatisation occurred most commonly in the FRA group, and PTSD in the ‘gaps’ group. These findings are broadly consistent with the view that psychogenic amnesia is commonly preceded by (i) a severe precipitating crisis (e.g. in a relationship or financial); (ii) a past or current history of clinical depression, and/or a range of other disorders; and (iii) a past or recent history of head injury or other neurological symptoms. In differentiating psychogenic from neurological amnesias, by far the most important factors were loss of personal identity, which occurred only in the psychogenic group, and neurological symptoms which, by definition, were always present in the neurological group. However, depression, a failure to recognise family members, family or relationship problems, financial or employment problems, and

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a history of PTSD, were all significantly more common in psychogenic amnesia. Surprisingly, a past history of head injury was also significantly more common in the psychogenic group; this may predispose some individuals to developing psychogenic amnesia at a later time of severe precipitating crisis (Kopelman, 2002a,b).

With regard to anterograde memory, some studies have previously reported impairment in psychogenic patients (e.g., Serra *et al.*, 2007), whereas others have not (e.g., Hennig-Fast *et al.*, 2008). On comparing psychogenic patients during or after the amnesic episode, we found that recall and recognition memory indexes were moderately higher at follow-up (by approximately 8 to 16 points), and this was statistically significant for verbal recall memory.

In terms of the retrograde amnesia itself, we found that fugue patients showed a ‘flat’ temporal gradient in recalling facts and episodes from their past during their acute amnesia. In contrast, both FRA groups showed a ‘reversed’ temporal gradient, as reported in some, but not all, previous studies (Kopelman *et al.*, 1994; Kritchevsky *et al.*, 1997, 2004; Tramoni *et al.*, 2008). This differentiating feature between fugue and FRA has not been previously reported, and might explain some of the discrepancies in the literature. Despite the use of neurological patients with chronic disorders (of several aetiologies), we obtained a conventional (‘Ribot’) gradient in our neurological group, consistent with that reported in previous studies of transient global amnesia (Kritchevsky *et al.*, 1988; Hodges and Ward, 1989; Bartsch *et al.*, 2011).

Interestingly, transient global amnesia can also be preceded by emotional stress or a significant life-event (Hodges and Warlow, 1990; Quinette *et al.*, 2006; Bartsch and Deuschl, 2010; Bartsch and Butler, 2013), and this is particularly the case in female patients (Quinette *et al.*, 2006). Moreover, recovery of autobiographical memories has been demonstrated in transient global amnesia (Hodges and Ward, 1989; Bartsch *et al.*, 2011), similar to that found in our fugue cases. On the other hand,

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transient global amnesia cases do not, by definition, show loss of personal identity, although they often show repetitive questioning (Hodges and Warlow, 1990; Bartsch and Deuschl, 2010) which was not present in any of our psychogenic cases. In transient global amnesia, there is a severe anterograde amnesia and a milder, graded retrograde amnesia (Bartsch and Butler, 2013), consistent with the presence of transient hippocampal (CA1) hyperintensities on diffusion weighted imaging (Bartsch *et al.*, 2006), whereas in psychogenic amnesia our findings clearly indicate a mild anterograde amnesia with a severe retrograde loss.

In general, management of the psychogenic cases consisted of (i) treatment of underlying depression, often with antidepressant medication; (ii) identifying and addressing underlying psychosocial concerns (relationship crises, financial issues, bereavement) and then, if memory had not recovered, (iii) a form of contextual interview moving from earlier, less stressful, to more recent memories (Brandt and van Gorp, 2006; McKay and Kopelman, 2009). An interview under sedation (Ruedrich *et al.*, 1985; Kopelman *et al.*, 1994) or hypnosis (Garver *et al.*, 1981; Mac Hovec, 1981) has been advocated; but contemporary treatments are more likely to incorporate techniques from cognitive behaviour therapy and acceptance/commitment therapy (Cassel and Humphreys, 2016).

At follow-up, we found a differential pattern of performance between our amnesic groups. In recalling personal semantic facts, the fugue group had improved to 'normal': their scores being very closely similar to those of the healthy controls across all time-periods. On autobiographical incidents, the fugue group again showed very striking improvement: they had not quite returned to 'normal', but were not significantly different from the controls' scores. Both the FRA groups also showed substantial improvement at follow-up, but theirs was a lesser improvement than the fugue group, and both continued to show a 'reversed' temporal gradient. In summary, the prognosis in psychogenic amnesia appears better than the previous literature suggests.

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Freud and Breuer (1895) argued that: “[In] psychical trauma...[memories were] intentionally repressed from...conscious thought and inhibited and suppressed.” But by the *Introductory Lectures*, Freud (1915/16) argued that repression was a purely unconscious process, with memories “inadmissible to consciousness”. Rivers (1918) (in the *Lancet* paper which influenced the novelist Pat Barker in her *Regeneration* novels) wrote of repression as a deliberate avoidance of emotional memories “to the point of suppression”, more consistent with the earlier Freud. Consistent with the notion of active avoidance or inhibition of memories, some of our patients made remarks such as: “It’s like a box locked away, and I don’t really want to open it” and “I put things in boxes...I know the memories are there...but I cannot get access to them.”

In a recent series of reviews, Markowitsch and colleagues (Reinhold and Markowitsch, 2009; Staniloiu *et al.*, 2010; Staniloiu and Markowitsch, 2012, 2014) have differentiated two contemporary models of psychogenic amnesia. One model (Markowitsch, 2002; Staniloiu and Markowitsch, 2014) has postulated that the release of stress-related hormones (following dysregulation of the hypothalamic-pituitary-adrenal axis) results in ‘amnesic block syndrome’, in which executive function may also be compromised. The other model (Kopelman, 2000, 2002a) has emphasised that the combination of a severe precipitating crisis, depressed mood, and past experience of a transient neurological amnesia, as in a minor head injury, can trigger ‘frontal’ inhibitory (or ‘control’) mechanisms in autobiographical memory retrieval. Awareness of personal identity (‘self’) and affective responsiveness can also be affected. Because medial temporal circuitry is apparently functioning normally, the person appears to acquire new anterograde memories, but this cannot be entirely normal because, when a fugue patient recovers, he/she is unable to recall memories from the period of ‘fugue’.

Anderson and colleagues have identified increased activation in the dorso- and ventral-lateral prefrontal cortex, with associated deactivation in medial temporal structures, during memory

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inhibition (Anderson and Green, 2001; Anderson *et al.*, 2004; Anderson and Hanslmayr, 2015). This affects the retrieval of autobiographical and aversive memories (Depue *et al.*, 2007; Noreen and MacLeod, 2014) with reduced hippocampal activation predicting later forgetting of unwanted memories (Levy and Anderson, 2012). Moreover, when memories are suppressed (compare Freud and Breuer, 1895; Rivers, 1918), there is also forgetting of preceding and subsequent memories, associated with disrupted hippocampal consolidation (Hulbert *et al.*, 2016). We postulate that these mechanisms are most likely to be triggered in particular psychosocial contexts, as described above. Anderson and Hanslmayr (2015) concluded that “Control mechanisms mediated by the prefrontal cortex interrupt mnemonic function and impair memory ... We are... conspirators in our own forgetting.”

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<u>Group</u>	<u>N</u>	<u>Gender ratio</u>	<u>Mean age</u>	<u>Age range</u>	<u>Mean BDI-II score ('during' episode for amnesia)</u>	<u>Duration of 'fugue'</u>	<u>Length of residual memory loss</u>	<u>First seen: time since onset</u>
<u>Fugue</u>	16	13M:3F	48.1±12.0	21-63	18.2±11.6	3.7 days ± 5.3 (Range=2 hrs to 21days)	2 hrs to 21 days	8<2 wks; 3<3 mths; 4<2yrs; 1>2 yrs post-onset.
<u>Fugue-to-FRA</u>	16	12M:4F	40.0±12.1	24-60	23.5±15.7	3.8 days ± 5.65 (Range 3 hrs to 18 days)	180 days to 'whole life'	5<3 mths; 7<2 yrs; 4>2yrs post-onset
<u>FRA</u>	16	11M:5F	43.5±12.8	27-66	15.1±11.7	Not applicable	<2 yrs to 'whole life'	4<3 mths; 8<2 yrs; 4>2yrs post-onset
<u>Gaps in memory</u>	5	3M:2F	46.4±9.7	33-56	26.0±18.2	Not applicable	5 hrs to 90 days	1<3 mths; 4>2yrs post-onset
<u>Neurological group</u>	21	15M:6F	56.1±12.2	28-76	10.5±9.7	Not applicable	No gap as such	3-18 months
<u>Healthy Controls</u>	14	9M:5F	54.9±14.3	25-72	3.4±3.8	Not applicable	Not applicable	Not applicable

Table 1. Diagnostic subgroups in psychogenic amnesia: gender ratios, age, BDI-II scores, plus pattern of amnesia, and time since onset when first seen in the psychogenic groups.

	χ^2	<i>p</i>	ϕ_c	Relative Risk	Odds Ratio
a) Features of Amnesia:					
Loss of personal identity	30.95	<.001	.65	2.40	-
Failure to recognise family	8.38	.004	.34	1.52	6.23
b) Background clinical and psychosocial factors:					
Depression	12.21	<.001	.41	1.68	8.98
Family/relationship problems	8.17	.004	.33	1.60	4.53
Finance/employment problems	9.20	.003	.35	1.55	8.45
Forensic history	6.25	.015	.29	1.52	-
PTSD	4.06	.053	.23	1.48	-
Somatisation history	2.59	.175	.19	1.48	-
Head injury	6.53	.012	.30	1.45	6.39
Childhood problems	2.41	.153	.18	1.27	2.83
Alcohol/substance misuse	2.41	.153	.18	1.27	2.83
Neurological history/symptoms	34.49	<.001	.68	0.38	-

Table 2. Clinical and psychosocial factors (a) and features of amnesia (b) in psychogenic versus neurological groups

a) Group	Premorbid IQ (NART-R)	Executive Function (FAS)	Verbal Recall	Visual Recall	Verbal Recognition	Visual Recognition
Control	106.9 (6.9)	47.4 (12.1)	87.6 (6.7)	108.7 (17.4)	97.4 (10.0)	91.3 (19.7)
Neurological	106.7 (11.6)	28.8 (12.4)	76.5 (13.7)	76.2 (12.6)	78.5 (17.4)	82.4 (12.1)
Fugue	108.0 (11.1)	33.5 (10.4)	83.3 (7.5)	104.3 (11.3)	88.9 (11.2)	91.1 (9.6)
Fugue to FRA	104.1 (7.9)	31.8 (10.9)	87.5 (19.7)	90.7 (26.8)	92.1 (22.4)	92.2 (19.5)
FRA	100.8 (9.6)	37.9 (9.6)	81.7 (20.3)	96.2 (26.2)	88.0 (20.5)	82.6 (20.5)
Gaps in memory	103.5 (15.8)	44.7 (17.8)	97.7 (29.1)	93.8 (20.3)	93.0 (19.7)	103.5 (28.0)

b)	Verbal Recall	Visual Recall	Verbal Recognition	Visual Recognition
During	85.7 (18.6)	93.4 (24.7)	88.9 (20.8)	87.9 (21.1)
Post-acute episode	102.0 (15.4)	101.6 (16.8)	104.0 (18.2)	96.6 (19.0)

Table 3. a): Mean scores for NART-R (premorbid IQ), FAS (verbal fluency) and anterograde memory tests during amnesic episode ($\pm 1SD$). One outlier in the ‘Gaps’ group has been excluded.
b): Mean anterograde memory index scores for ‘during’ and ‘post’ acute psychogenic amnesia groups combined.

Figure Legends

- Figure 1 Clinical and psychological factors in the controls and psychogenic subgroups
- Figure 2 Clinical and psychosocial factors: Psychogenic vs. Neurological groups
- Figure 3 Personal semantic memory during the amnesic episode (A) and at follow-up (B)
- Figure 4 Autobiographical episodic memory during amnesia and at follow-up
- Figure 5 Personal semantic and autobiographical memory: controls, psychogenic group ('during' amnesia and at follow-up) vs. neurological memory-disordered patients

FIGURE 1

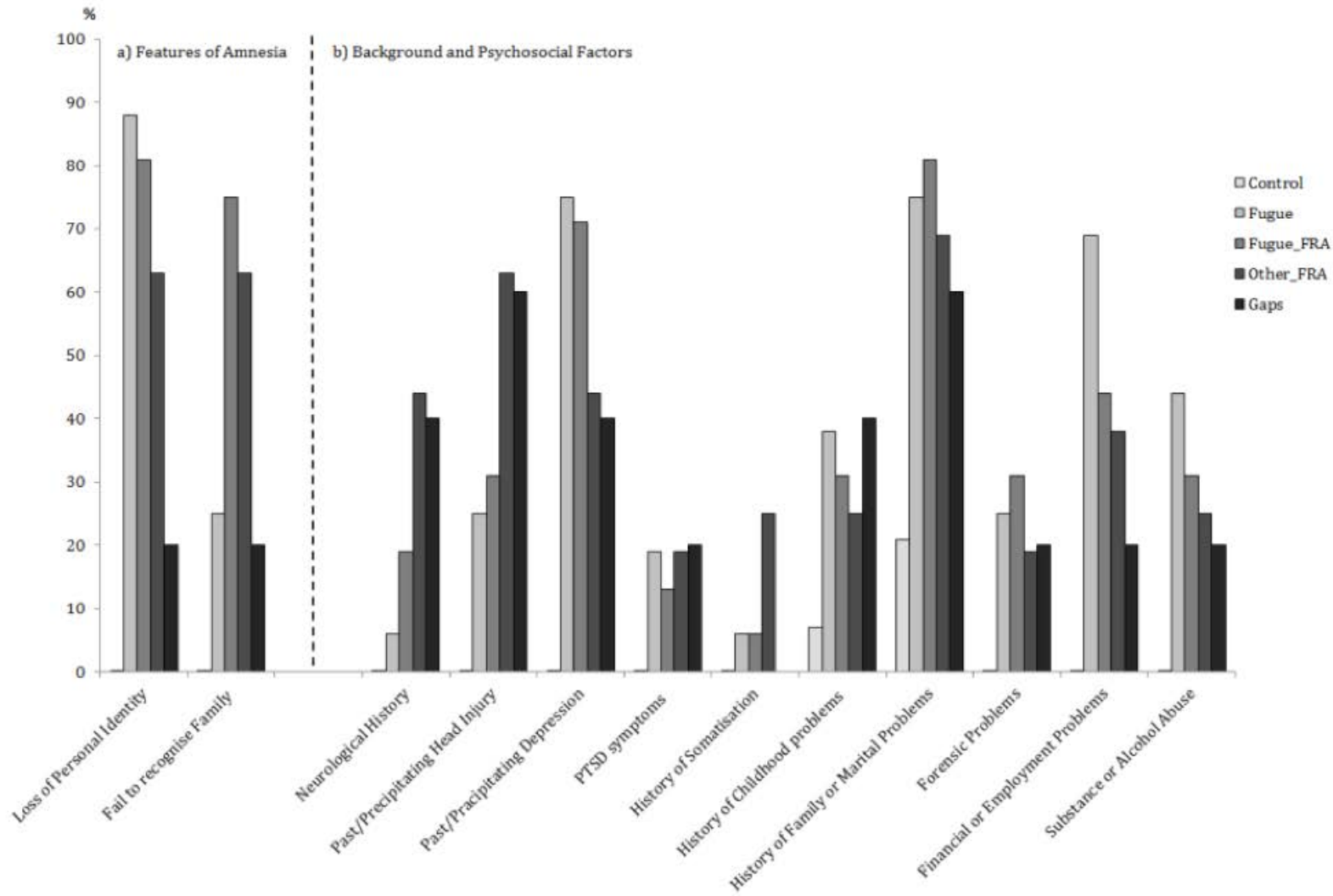


FIGURE 2

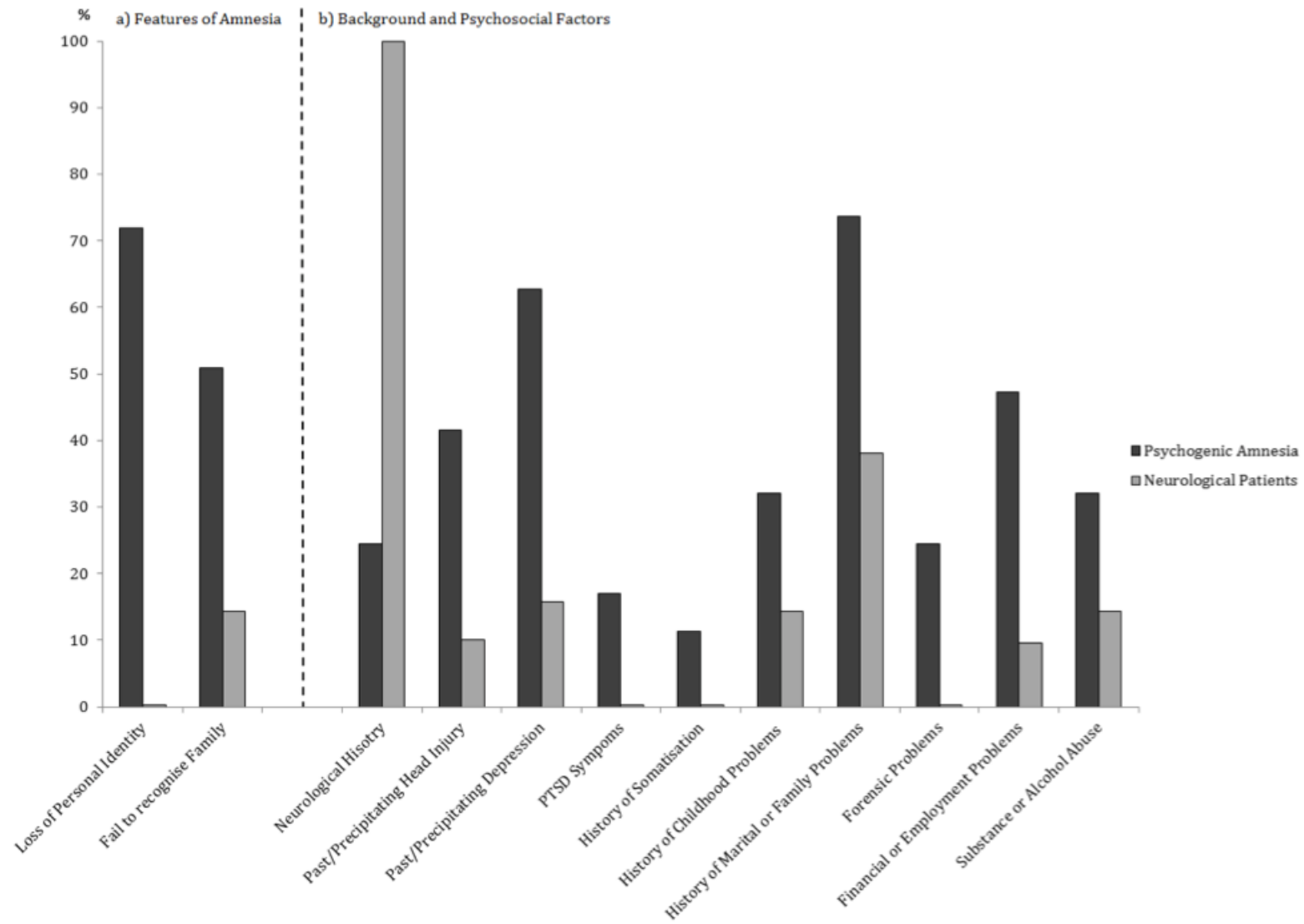


FIGURE 3

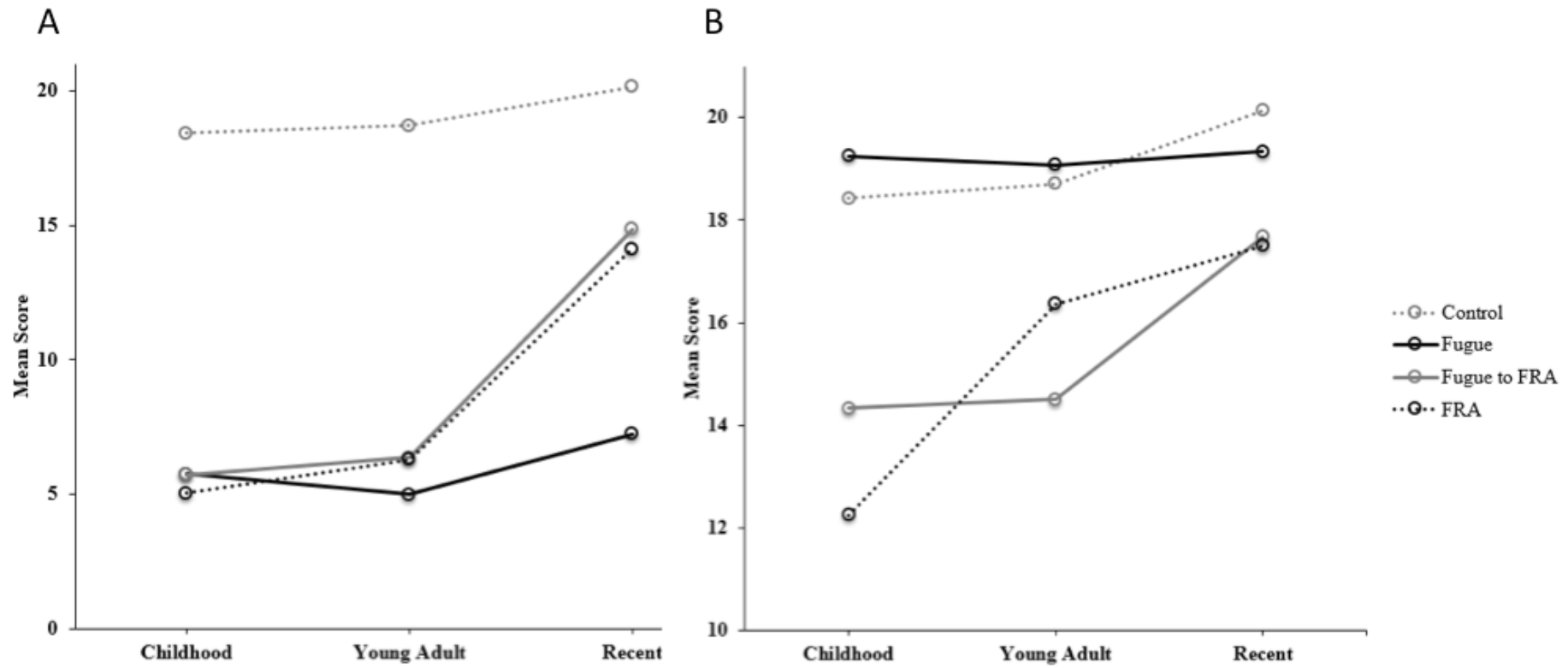


FIGURE 4

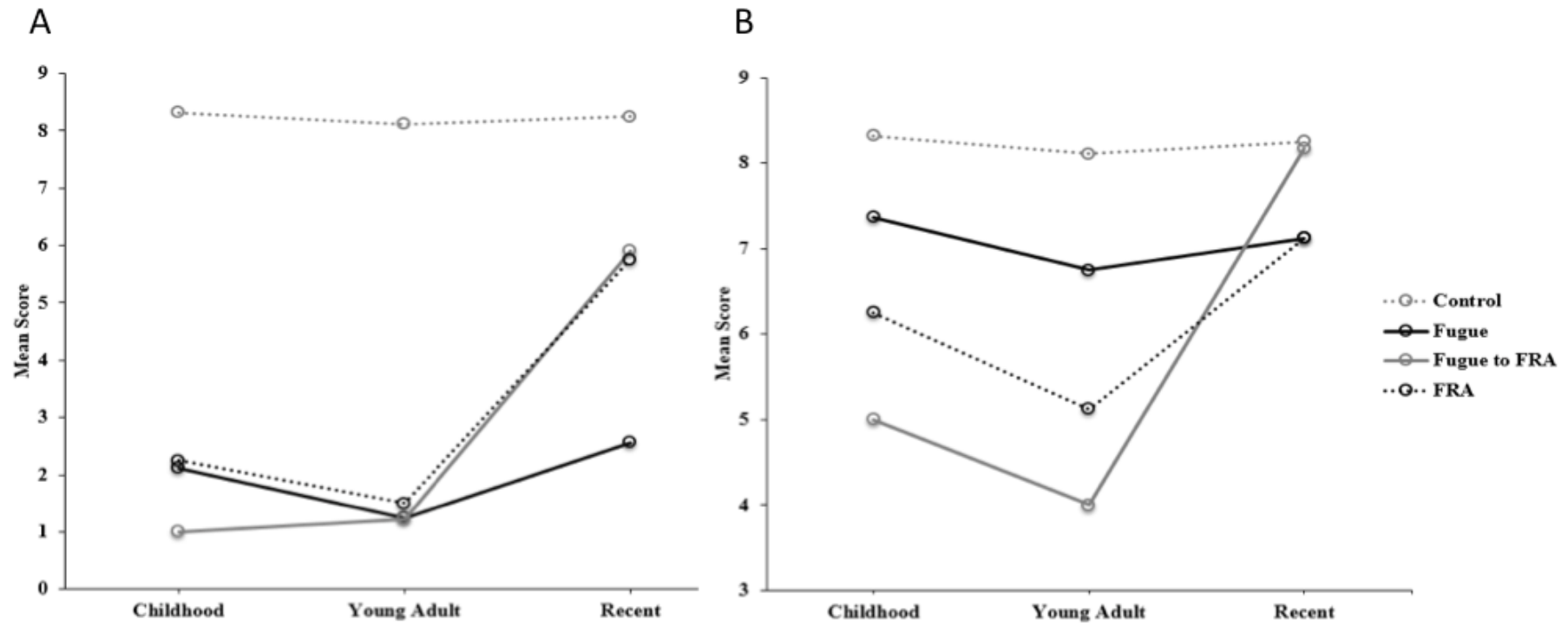
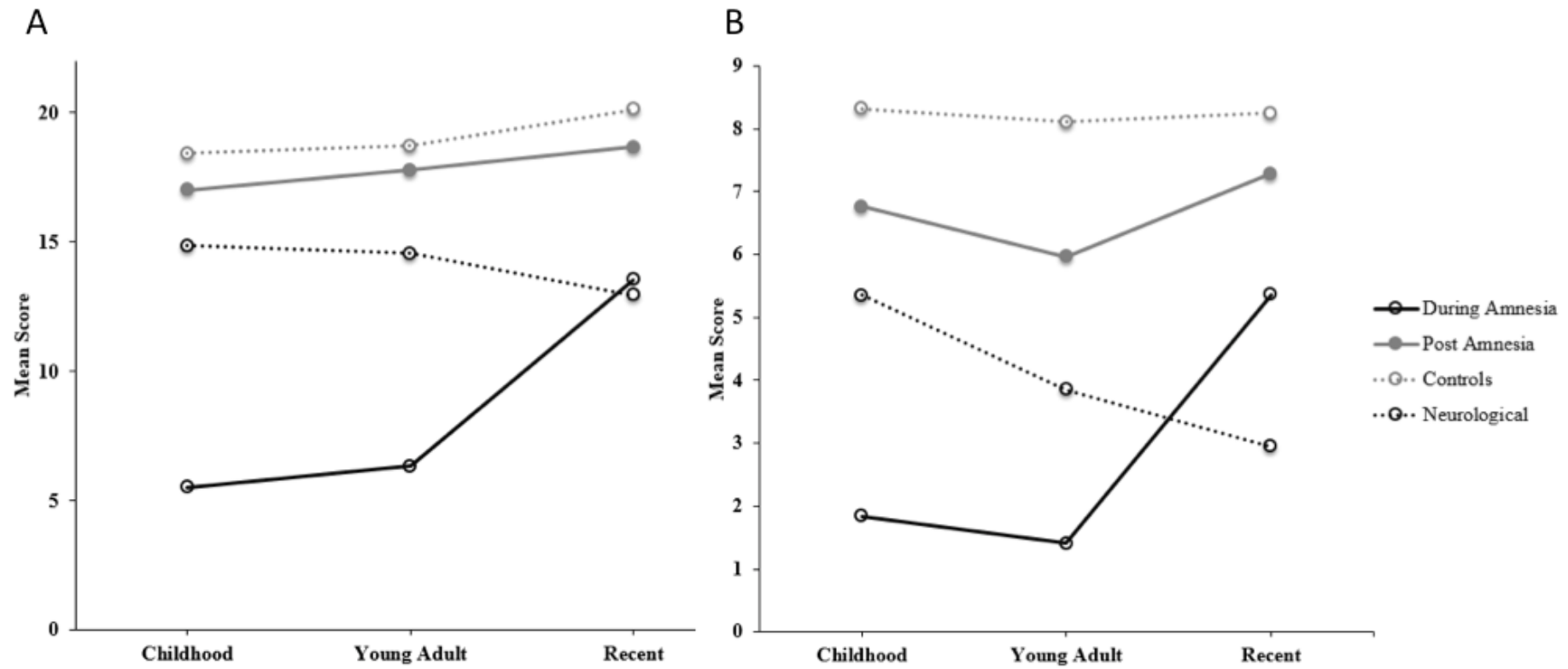


FIGURE 5



Supplementary Material

Psychological and Psychosocial Factors recorded from patients' clinical records

Was there a loss of personal identity?

Any previous incidences of psychogenic amnesia?

Any neurological history?

Past or precipitant head injury?

Past or precipitant depression?

PTSD symptoms?

History of somatisation?

Psychological problems in childhood?

Did patient fail to recognise their family members?

Marital problems prior to index incident?

Family problems?

Past or precipitant forensic problems?

Financial problems prior to index incident?

Employment problems prior to index incident?

History of alcohol or other substance abuse?
