

Disorientation in amnesia

A confusion of memory traces

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Summary

Disorientation is a common phenomenon in delirium and amnesia. It is thought to have an obvious explanation, i.e. disoriented patients fail to store the information crucial for the maintenance of orientation. In this study, we explored whether disorientation was indeed associated with a failure to learn new information or rather with a confusion of information within memory. Twenty-one patients with severe amnesia were examined. Orientation was tested with a 20-item questionnaire. Two runs of a continuous recognition task were used to test the ability to acquire information (first run of the task) and the tendency to confuse the temporal context of information acquisition (comparison of the second with the first run). We found that orientation was much

better predicted by the measure of temporal context confusion ($r = 0.90$) than by the ability to simply acquire information ($r = 0.54$). Superimposition of neuroradiological scans demonstrated that increased temporal context confusion was associated with medial orbitofrontal or basal forebrain damage; patients with normal levels of temporal context confusion did not have damage to these areas. We conclude that disorientation more often indicates a confusion of memory traces from different events, i.e. increased temporal context confusion, than an inability to learn new information. Disorientation appears to reflect primarily a failure of the orbitofrontal contribution to memory.

Keywords: temporal order amnesia; disorientation; confusion; frontal lobes; orbitofrontal cortex; memory

Abbreviations: CVLT = California Verbal Learning test; IR = item recognition; TCC = temporal context confusion

Introduction

Disorientation to time, place and situation, rarely also to person, is a common finding in clinical practice. Disorientation is a regular component of acute confusional states (delirium) (Horenstein *et al.*, 1967; Chédru and Geschwind, 1972; Mesulam *et al.*, 1976; Devinsky *et al.*, 1988) and is sometimes present in dementia (Cummings and Benson, 1992) and amnesia. The mechanism of disorientation appears to be obvious: clinical wisdom holds that disoriented subjects cannot store new information and therefore fail to continuously update their knowledge about time and the environment (Benton *et al.*, 1964; High *et al.*, 1990). However, there is an alternative possibility as schematized in Fig. 1: normal memory function demands not only that information has been stored but also that the temporal order among pieces of information is maintained (Fig. 1A). Disorientation might not only ensue from a failure to simply store information (Fig. 1B) but also, and possibly more so, if a subject did store information, but confused the temporal sequence of information within memory (Fig. 1C) (Von

Cramon and Säring, 1982; Baddeley and Hitch, 1993). This would make it difficult to realize what piece of stored information pertained to the present situation. In a recent study we found that this type of memory failure sets spontaneously confabulating patients apart from other amnesic patients (Schnider *et al.*, 1996b).

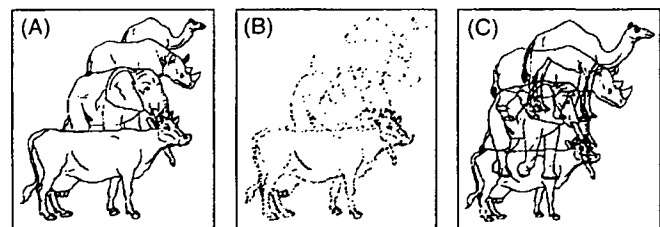


Fig. 1 Types of memory failure: schema illustrating (A) normal storage of both item and temporal sequence information in memory, (B) failure to retain new information in memory; and (C) confusion of the temporal sequence of information acquisition within memory despite storage of the information itself.

In the present study we explored the possibility that disorientation in amnesia is associated with a failure to learn new information or an increased tendency to confuse the temporal context of information acquisition. Because we looked for a common mechanism of disorientation, patients were included irrespective of the aetiology of their amnesia.

Patients and methods

Twenty-one amnesic patients hospitalized for neuropsychological rehabilitation participated in the study. Aetiologies of amnesia were as follows: traumatic brain injury ($n = 8$); haemorrhage and surgery of an aneurysm of the anterior communicating artery ($n = 5$) or right posterior communicating artery ($n = 2$); herpes simplex encephalitis ($n = 2$); surgery of an invasive left olfactory meningioma ($n = 1$); Wernicke–Korsakoff syndrome ($n = 1$); right frontal haemorrhage ($n = 1$); left thalamic infarction ($n = 1$). All patients' amnesia was evident in everyday behaviour and was confirmed with several memory tests as documented in our previous study (Schnider *et al.*, 1996b). However, patient selection was based on performance in the California Verbal Learning test (CVLT; Delis *et al.*, 1987). Because all patients finally judged as disoriented had a long delay free recall (of ≤ 4 in the CVLT, only patients with similarly deficient recall were included. All patients were mobile on the ward throughout the day. Only patients who had been in our unit for at least 2 weeks were included to ensure that all patients had been living in a similar setting and had thus received a similar amount of information to help orientation. Patients were excluded if they had insufficient attention (digit span < 5) or another cognitive deficit precluding participation in the experiment (e.g. aphasia, visual agnosia). The tests reported here were performed 75 ± 55 (17–270) days after the occurrence of brain damage. Fifteen age- and education-matched controls with no history of neurological or psychiatric illness (mostly family members of patients) were also tested. All subjects gave their informed consent to being tested.

Orientation

The orientation test described by Von Cramon and Säring (1982) was used. This is in the form of a questionnaire designed for German speaking subjects. It contains questions that are particularly appropriate for hospitalized patients and comprises five questions for each of four domains of orientation: (i) orientation to person: name, age, profession, citizenship, eye colour; (ii) orientation to place: city, name of building, unit or floor, approximate direction of home town, county; (iii) orientation to situation: reason for being here, type of treatment, sources of support, name of a person on the ward, party covering the costs of the sojourn; (iv) orientation to time: day of the week, date, month, year, time. A correctly oriented subject will give at least four correct answers for domains (i) to (iii) and at least three

correct answers for domain (iv). The total number of correct answers is ≥ 15 in correctly oriented subjects (Von Cramon and Säring, 1982).

Item recognition, temporal context confusion (experiment)

Free recall ('Do you remember the words that I told you before?') requires both that the demanded information has been stored and that it can be retrieved from memory. All patients in this study failed to recall previously learned words. Pure information storage is better reflected by the ability to recognize previously learned information (Lezak, 1995). Since this study aimed to juxtapose the impact of failed storage of information and of increased confusion of the temporal context of information acquisition on disorientation, it was desirable to test temporal context confusion with a recognition task too, so that the two processes could be directly compared. The following experiment, which was more extensively discussed in a previous article (Schnider *et al.*, 1996b), tested both processes with two components of the same recognition task:

Run 1: item recognition (IR)

To test pure information storage, a continuous recognition task of design similar to the recognition tests of Sturm and Willmes (1995) for nonsense stimuli was composed with 120 meaningful, concrete drawings from Snodgrass and Vanderwart (1980). The picture series consisted of six series with 20 pictures each. Each series contained eight items that appeared in all six series (thus, they were repeated five times after initial presentation) and 12 distracter items that were not repeated in other series. Each picture was presented on a computer screen for 2 s. For each picture the subjects were requested to answer the question: 'Have you already seen precisely *this* picture in *this* run?'. Answers were recorded by the examiner pressing the appropriate response key and immediately followed by presentation of the next picture. According to Sturm and Willmes (1995), the item recognition score was calculated as: $IR = \text{hits} - \text{false positives}$. The maximum score was therefore 40 (40 hits, no false positives).

Run 2: temporal context confusion (TCC)

One hour after the recognition task (run 1), a second run was made with precisely the same design. For this run, target items were replaced so that eight distracter items from the first run now served as the target items, while the target items from the first run now ranked among the distracters. Subjects were instructed to 'forget that [they] had already taken a similar test before' and were requested to answer the question: 'Have you already seen precisely *this* picture in *this* run?' for each picture. The central idea behind the experiment was that false familiarity with a distracter item

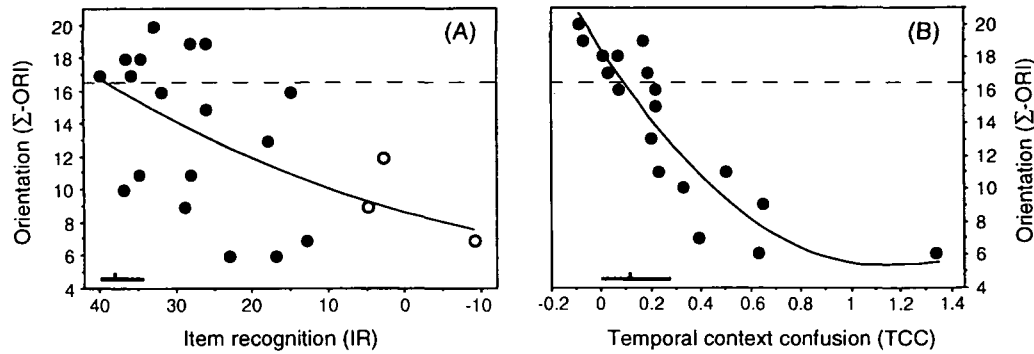


Fig. 2 Amnesic patients' association of total orientation score (Σ -ORI) with (A) item recognition (IR) and (B) the temporal context confusion (TCC). Open circles indicate patients with IR in the chance range; in these patients, TCC was not determined. The dashed horizontal lines separate patients with disorientation in at least one domain from normally oriented amnestics. The bars in the lower left corners indicate the controls' range of performance (maximal to minimal values) and the controls' mean.

Table 1 Association of orientation scores with item recognition (IR) and temporal context confusion (TCC)

Variable	IR	TCC
Σ -ORI	0.54*	0.90***
TIME-ORI	0.38	0.78**
PLACE-ORI	0.57*	0.79**
SIT-ORI	0.55*	0.84***

Association of orientation scores with IR and TCC. Numbers indicate second order polynomial regression coefficients. Orientation measures: Σ -ORI = total orientation score; TIME-ORI = time orientation score; PLACE-ORI = orientation to place score; SIT-ORI = orientation to situation score. Significance levels: * $0.05 > P > 0.01$; ** $0.01 \geq P > 0.0001$; *** $P \leq 0.0001$.

(i.e. a false positive response) was based on an inability to distinguish between the item's previous occurrence in the first rather than the second run (irrespective of whether it has been a target or a distracter in the first run), i.e. on temporal context confusion (TCC). Thus, TCC was defined as the relative increase of false positives in the second over the first run, i.e. $TCC = (FP_2 / Hits_2) - (FP_1 / Hits_1)$, where FP_1 and FP_2 = false positives in run 1 and 2, respectively; $Hits_1$ and $Hits_2$ = hits in run 1 and 2, respectively. Since this experiment could measure temporal context confusion only if a subject was able to store information at all, run 2 was made only with subjects who had performed significantly above chance in run 1 ($d' > 1.64$, Brophy, 1986). Two patients with herpes simplex encephalitis and one patient with traumatic brain injury did not meet this criterion.

Lesion analysis

Most patients had several CT scans. An MRI was available for four patients. An attempt was made to account for the different lesion types: in patients with traumatic brain injury, all haemorrhagic lesions visible in the early scans (after removal of subdural or epidural haematomas in two patients)

were taken into account because each parenchymal haemorrhage is likely to indicate an area of axonal damage (Eisenberg and Levin, 1989). Lesions were also taken into account if they were subsequently invisible in later scans. With all other aetiologies, the scan performed closest in time to our experiment was analysed to prevent overestimation of the lesion area due to perifocal oedema. Lesions were reconstructed with the templates of Damasio and Damasio (1989) and referred to a composite axial slice containing the hippocampus, amygdala and basal forebrain and to the midsagittal plane (see Fig. 3). The lesion areas were superimposed in a commercial drawing program. Four patients had CT and MRI scans with no visible focal brain lesion (clipping of an anterior communicating artery aneurysm, $n = 1$; Wernicke-Korsakoff syndrome, $n = 1$; traumatic brain injury, $n = 2$).

Results

Amnestics versus controls

Figure 2 shows the performances of the patients and controls. Item recognition discriminated much better between amnestics and controls ($t(34) = 4.2$, $P = 0.0002$; Fig. 2A) than TCC ($t(31) = 1.9$, $P = 0.06$; Fig. 2B). The IR and TCC scores were not significantly correlated ($P > 0.05$) either in the controls ($r = -0.48$) nor in the amnestics ($r = -0.28$).

Determinants of disorientation

Eleven patients were disoriented to time, place and situation, three patients were disoriented only to time, and seven patients were normally oriented. The following analysis was limited to the amnestics to determine the contribution of IR and TCC to disorientation. Because all patients were oriented to person, this domain of orientation was omitted from further analysis. Highest regression coefficients with orientation scores were obtained using second order polynomial

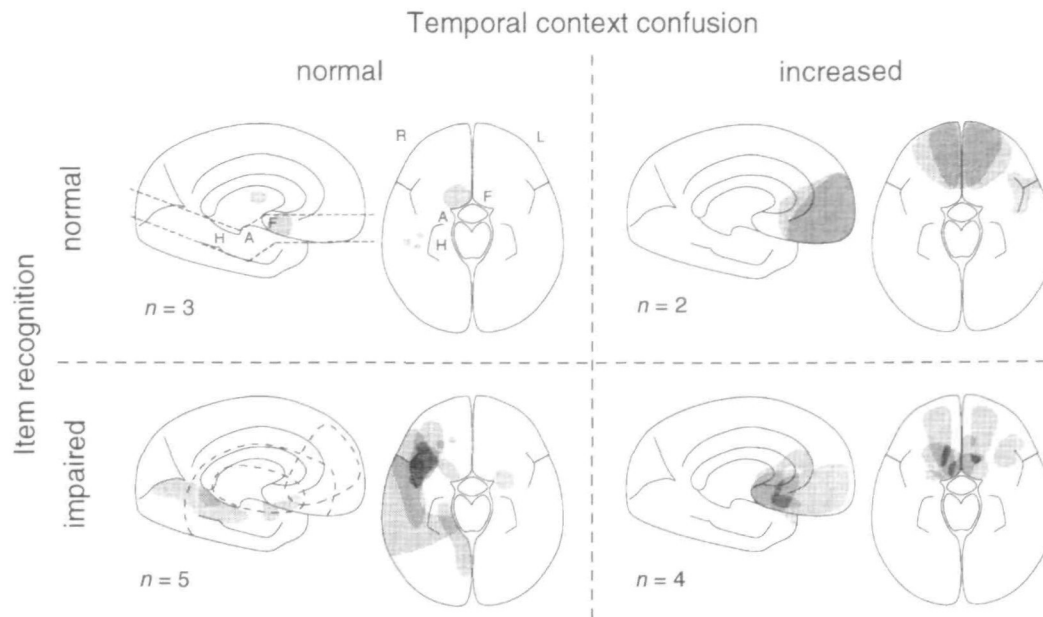


Fig. 3 Lesion reconstruction showing the projection of lesions to the midsagittal plane and a combined axial plane encompassing the hippocampus (H), the amygdala (A), and the orbitofrontal area (including basal forebrain, F) as indicated in the upper left design. Patients are separated according to whether their item recognition and temporal context confusion were within ('normal') or outside the controls' range ('impaired' IR, 'increased' TCC). In the sagittal plane, shaded areas indicate lesions close to the midline, empty polygons with dashed lines indicate lateral hemispheric lesions. 'n' indicates the number of patients in the respective group.

regression rather than simple regression. All domains of orientation were much better predicted by TCC than by IR (see Fig. 2 and Table 1).

The total number of correct answers (Σ -ORI in Table 1) did not significantly correlate with the following parameters: days after brain injury ($r = 0.23$), age ($r = -0.06$), number of years at school ($r = -0.08$); or with several measures of frontal lobe function: verbal fluency (Thurstone and Thurstone, 1963), $r = 0.29$; figural fluency (Regard *et al.*, 1982), $r = -0.20$; colour-word interference (Stroop, 1935), $r = 0.14$.

Lesion analysis

Patients were separated according to whether their IR and TCC were within or outside the range of the controls. By accepting this broad range of 'normality', classification in the 'impaired' group has a high specificity for true impairment while there is a risk that some patients with a true impairment would be classified as 'normal'. This was the case with three amnesic patients who scored in the 'normal' range on both IR and TCC. The three patients with chance IR scores were excluded from this analysis because their TCC was not determined. Patients with increased TCC and normal IR ($n = 2$) had medial orbitofrontal lesions sparing the basal forebrain (Fig. 3). Patients with impaired IR but normal TCC ($n = 5$) had diverse lesions sparing both the medial orbitofrontal cortex and the basal forebrain. Patients with

both impaired IR and increased TCC ($n = 4$) had lesions that mostly involved the basal forebrain.

Discussion

Our results indicate that disorientation in amnesia is based primarily on a confusion of information within memory rather than a lack of stored information. Although severe failure to store new information was associated with disorientation, increased temporal context confusion predicted disorientation much better (Table 1 and Fig. 2). Although correlations do not prove a causal link, our study strongly suggests such a link: first, this study prospectively tested the possibility that the two examined mechanisms of memory contributed to orientation, a possibility which was *a priori* reasonable; secondly, other measures of frontal lobe function did not correlate with orientation, indicating a specificity of temporal context confusion.

It has been surmised that disorientation after brain damage reflects anterograde and retrograde amnesia (Benton *et al.*, 1964; High *et al.*, 1990), i.e. an insufficient amount of information in memory to maintain orientation (Fig. 1B). This explanation cannot account for the observation that disoriented patients' responses to questions of orientation may vary from one interview to another; the answers may be correct at one time and wrong at other times (Daniel *et al.*, 1987). Our results suggest that the main problem of disoriented patients is a confusion of memory traces from

diverse events rather than a lack of information in memory. While a healthy person normally has a feeling for the recent flow of information and does not have any difficulty in realizing what acquired knowledge refers to the present (Fig. 1A), a disoriented patient may be unable to distinguish intuitively between knowledge acquired some minutes ago and knowledge acquired some days, months, or even years ago (Fig. 1C). The patient may therefore confuse the date, place and the reason of his being in a particular place and his responses may vary from one occasion to the other. Incorrect responses to questions of orientation may reflect a subject's problem in selecting the currently correct answer from memory rather than a lack of this knowledge.

This study was designed to seek a common mechanism of disorientation in amnesia and therefore included patients with diverse types of brain damage. Certain aetiologies of amnesia were not represented in our study group. Notwithstanding these caveats, our data suggest that increased temporal context confusion emanates from prefrontal, especially medial orbitofrontal, damage or disconnection. Conversely, a decreased capacity to store and subsequently recognize new information appears to have less anatomical specificity as it may result from lesions in diverse locations (Fig. 3). Basal forebrain lesions appear typically to produce a combination of these two types of memory failure. Our finding of a functional and anatomical dissociation between item recognition failure and temporal context confusion is in agreement with earlier studies on temporal order recognition (Squire, 1982; Milner *et al.*, 1985; Hunkin and Parkin, 1993).

Our study does not definitively determine whether increased temporal context confusion reflects a failure of the process of information storage or information retrieval. In our opinion, defective retrieval is unlikely because it would similarly affect recollection of recent and remote information. However, many disoriented patients and many patients with spontaneous confabulations—which are also accounted for by increased temporal context confusion (Schnider *et al.*, 1996*b*)—readily give precise accounts of remote events (Schnider *et al.*, 1996*a*). We suggest that increased temporal context confusion is mainly due to a specific defect of information storage, i.e. a failure to co-encode temporal order information. Temporal order information should not be conceived of as separate from item information but rather in terms of the saliency that recent information may attain in memory, as schematized in Fig. 1. This saliency, which distinguishes recent from remote information, may be determined by the behavioural relevance attributed to new information (Schnider *et al.*, 1996*a*). Neurons in the orbitofrontal cortex have been shown to react specifically to stimuli of behavioural significance (Rosenkilde *et al.*, 1981). We have previously suggested that defective temporal labelling of information, resulting in increased temporal context confusion, may result from damage of the circuit connecting the amygdala, the dorsomedial thalamic nucleus, and the orbitofrontal cortex, whereas failed retention of information in memory, resulting in defective item

recognition, may result from an interruption of the classic Papez circuit, i.e. the circuit connecting the hippocampus with the anterior thalamic nucleus (Schnider *et al.*, 1996*a*). Both circuits have multiple, spatially close connections in the anteromedial thalamus (e.g. mamillo-thalamic tract, ventral amygdalo-fugal pathways) and basal forebrain (e.g. septum verum, ventral striatum); a lesion in this area may thus interrupt either limbic circuit and produce either type of memory failure.

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