# Dopamine inhibition and the adaptation of behavior to ongoing reality

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Received I6 November 2003; accepted I5 December 2003

DOI: I0.1097/01.wnr.0000115961.76286.18

Spontaneous confabulation is a rare memory disorder resulting from orbitofrontal damage or disconnection. Patients act on the basis of memories that do not pertain to the current situation, and are disoriented. No medical treatment is known. Recent studies suggest that subcortical dopaminergic structures are involved

in the selection of currently relevant memories. We present a patient who regained the ability to adapt thought and behavior to ongoing reality when treated with risperidone, a dopamine antagonist. *NeuroReport* 15:709–712 © 2004 Lippincott Williams & Wilkins.

Key words: Dopamine; Reality monitoring; Risperidone; Spontaneous confabulation

# **INTRODUCTION**

Spontaneous confabulation reflects a profound derangement of thought [1-3]. Patients act according to previous habits ignoring current reality. They justify their acts with confabulations which can mostly be traced back to true events in their past [3]. Spontaneous confabulation appears to emanate from a failure to suppress (de-activate) memories that do not pertain to ongoing reality [4]. Recovery is associated with restoration of this suppression capacity [5]. A recent imaging study indicated that suppression is conveyed by subcortical structures commonly considered components of the dopaminergic reward system [6]. This finding, together with evidence from other studies [7,8], suggests that modulation of subcortical dopaminergic transmission may be involved in the adaptation of thought and behavior to ongoing reality. Here, we present a patient whose confabulatory state was reverted by a dopamine antagonist.

# PATIENT AND METHODS

Case report: S.C., a Swiss journalist, had taken an early retirement and spent parts of the year in Bordeaux, France, playing golf. After a cerebral bleed from an anterior communicating artery aneurysm he was transferred to the University Hospital Bern, Switzerland, for surgical treatment. Computed tomography (CT) revealed an extensive lesion of the left basal forebrain (Fig. 1a). After recovery from coma S.C. started to produce spontaneous confabulations and was disoriented. Our hospital was mistaken for a hotel in Bordeaux. He complained about the room service and claimed that smoking and drinking was definitely allowed on his last stay with us. S.C. repeatedly tried to find his golf

equipment and expected to find a golf course around the house. He asked his wife not to drive 400 miles between 'Bordeaux' and his hometown in Switzerland every day. Our patient identified one of the nurses as the godchild of his wife and addressed her with the familiar 'du' form. Permanent supervision was necessary to prevent him from disappearing.

Methods: Given the lack of clinical improvement of our patient after 4 months, we decided to treat him with risperidone, a blocker of D2 receptors, which is approved for the treatment of organic confusional states in Switzerland. To evaluate medication effects, we documented the clinical course and undertook repeated neuropsychological testing. Four days after the administration of the baseline continuous recognition test, risperidone was initiated at a dose of 0.5 mg twice daily. This dose was doubled to 1.0 mg twice daily after 7 days of active treatment (Fig. 1b). We repeatedly applied the continuous recognition test, which had reliably distinguished between spontaneous confabulators and non-confabulating amnesics in our previous studies [4], and which precisely paralleled the clinical course of spontaneous confabulation [5]. This test measures the ability to distinguish between memories relating to now (repetitions within a run of the recognition task) and memories relating to the past (repetitions from a previous run). The task consisted of two runs of a continuous recognition task composed of exactly the same picture set, but arranged in different order in each run. Runs were separated by a 20 min rest interval. The patient's task was to indicate picture recurrences only within the ongoing run and to ignore familiarity from previous runs. Thus, the first run presents novel items and measures the ability to learn

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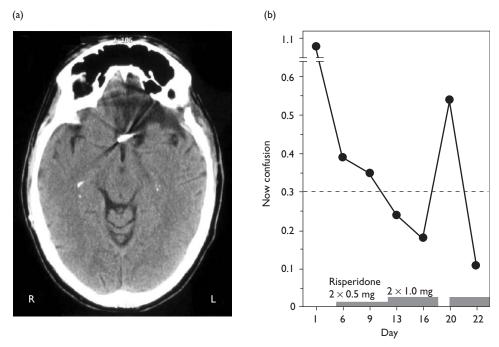


Fig. 1. (a) CTscan 2 months after aneurysm bleeding, showing an extended lesion of the left basal forebrain and orbitofrontal cortex. (b) Performance in the reality monitoring task measuring the ability to suppress currently irrelevant memories [4].

**Table I.** Results of repeated neuropsychological testing prior to treatment (baseline) and during risperidone intake. Day numbers refer to time scaling of Fig. lb.

	Baseline (day I)		Treatment (day 9)		Treatment (day I6)		Treatment (day 22)	
	Score	T-score <sup>a</sup>	Score	T-score	Score	T-score	Score	T-score
Executive functions								
Wisconsin Card Sorting Test								
Categories	0	< 24	0	< 24	0	< 24	0	< 24
Perseverative Errors	91	< 20	93	< 20	93	< 20	93	< 20
Word fluency								
Correct	15	40	12	35	12	35	18	44
C: Perseverations/rule breaks	0	> 55	1	55	4	< 27	2	49
Design fluency								
Total	10	24	П	25	16	30	18	31
Correct	10	26	10	26	16	33	15	30
Stroop test								
C: seconds	66	< 20	42	37	55	21	45	33
Errors	0	>41	1	41	0	>41	2	26
Memory assessment								
Rey auditory verbal learning test								
Learning	23	25	22	24	27	29	23	25
Short delay recall	3	25	1	< 20	0	< 20	0	< 20
Long delay recall	3	24	0	< 20	0	< 20	0	< 20
Recognition minus false positives	4	21	4	21	3	< 20	3	< 20
Orientation questionnaire								
Von Cramon and Säring (correct/total) <sup>b</sup>	0.70		0.75		0.90		0.90 (day 19: 0.60)	

 $<sup>^{</sup>a}$ Mean = 50, s.d. = 10.

and recognise new information. In the second run, all items are already known; the subject now has to distinguish between memories relating to the ongoing reality of the current second run and irrelevant familiarity from the preceding presentation of items in the first run. As in previous studies, the confusion of ongoing reality (comparison of the second run with the first run) was calculated as: Now confusion =  $FP_2/Hits_2-FP_1/Hits_1$ , where  $FP_1/2=false$ 

positive responses in run 1 and 2;  ${\rm Hits}_{1,2} = {\rm correct}$  positives (recognition of picture recurrences within the ongoing run) in run 1 and 2. In our previous studies, all spontaneous confabulators (but no non-confabulating amnesic) had values > 0.3 [4,5]. In addition to the continuous recognition task, the patient was repeatedly tested for orientation, executive, and memory functions. Baseline testing was followed by assessments under medication (Table 1).

<sup>&</sup>lt;sup>b</sup>Values < 0.75 are defined as pathological.

#### **RESULTS**

Before treatment, performance in the task corresponded to a severe state of spontaneous confabulation. Under risperidone his state improved: he produced markedly less confabulations and his tendency to leave the hospital decreased. After 11 days under medication (day 16 in Table 1 and Fig. 1b), orientation was normal and he correctly cited the reason for his current hospitalisation. S.C. was now convinced that he had recently moved from a French hospital to Bern. The clinical improvement was accompanied by normalization in the continuous recognition task and the orientation questionnaire, whereas performance in other neuropsychological measures remained stable (Fig. 1b, Table 1).

Since antipsychotics are potentially hazardous for recovery after brain damage [9], we decided to stop medication after 18 days, in order to ascertain that the clinical improvement was indeed due to the medication rather than spontaneous recovery. The next day, S.C. was agitated, disoriented, and produced new confabulations in parallel to deteriorating performance in the reality monitoring task (Fig. 1b). Medication was resumed and again induced marked clinical improvement. S.C. was dismissed from hospital and participated in an out-patient rehabilitation program, making the trip from his home town to Bern on his own.

### **DISCUSSION**

Our patient, who produced spontaneous confabulations, confused ongoing reality, and remained severely disoriented for 4 months, rapidly stopped confabulating and became oriented after risperidone intake. The improvement was dose dependent and was accompanied by improving performance in a task known to parallel the course of spontaneous confabulation. When risperidone was stopped, spontaneous confabulation reappeared; reintroduction of the medication again induced marked improvement. This case demonstrates that inhibition of the dopaminergic system can foster the ability of spontaneous confabulators to adapt thought and behavior to ongoing reality.

Dopamine antagonists are commonly used to alleviate psychotic thinking (delusions, hallucinations). It has recently been suggested that dysregulation of dopamine transmission leads to aberrant assignment of salience to external objects and internal representation [10]. Our patient's misidentification of one of the nurses as a godchild might represent an example of false assignments of internal representations and beliefs. This kind of delusional misidentification is discussed in the literature as Frégoli syndrome and has been associated with various psychiatric and neurological diagnoses [11]. However, such misidentification does not have a consistent association with spontaneous confabulation [3]. In the patient presented here, it did not show a complete alleviation under antidopaminergic treatment. This suggests neural mechanisms different from those involved in spontaneous confabulation. Antipsychotics are assumed to dampen salience of inappropriate ideas and the degree to which they occupy the mind. Therapeutic effects with gradual and incremental response to D2 blocking were assumed to reflect compensatory cognitive mechanisms which may develop after dampening of psychotic thinking. Our patient, however, showed an immediate and dose dependent effect of D2 blockage. This makes compensatory cognitive strategies an unlikely explanation and suggests direct anti-dopaminergic effects on anterior limbic and connected subcortical neural networks. These brain areas are typically affected in patients with spontaneous confabulations. S.C.'s immediate deterioration after suspending medical treatment for one day might be explained by the fast dissociation of risperidone from the D2 receptor, a pharmacokinetic property of atypical antipsychotics [12]. The precise locus of neuroleptic drug action is still unknown. Possible areas of action are subcortical structures, in particular, the striatum. Indeed, a specific type of psychosis, induced by psylocibin in healthy volunteers, appears to be associated with an elevation of dopamine in the ventral striatum [8]. The ventral striatum receives direct afferents from the posterior orbitofrontal cortex. This brain region is typically damaged or disconnected in spontaneous confabulators [3,5,13].

Our previous studies indicated that the inability to adapt thought and behavior to ongoing reality, the hallmark of spontaneous confabulation, emanates from deficient suppression of mental associations (activated memories) that do not pertain to now [14]. Evoked potential data suggested that this suppression precedes conscious recognition of its content and, thus, defies immediate voluntary control [15]. A PET study with healthy subjects demonstrated involvement of subcortical structures that are known to be part of frontal-subcortical loops and which represent dopaminergic components of the brain's reward system: ventral striatum, caudate, substantia nigra and medial thalamus [6,16]. We suggest that the main locus of action of risperidone in our patient lies within these structures. The influence of anti-serotonergic drug effects remains unclear. It has been shown that 5HT<sub>2</sub> transmission mainly influences mesocorticolimbic rather than nigrostriatal dopaminergic function [14]. If our hypothesis is correct that adaptation of thought to ongoing reality depends on frontosubcortical loop activity [3,6], anti-serotonergic drug effects may have played a minor role.

What might be the function of dopaminergic inhibition in reality monitoring? The role of the orbitofrontal cortex and its subcortical connections in behavioral adaptation to rewarding and non-rewarding stimuli is well known from an extensive corpus of clinical and animal studies [17]. Phasic depression of dopaminergic neurons in the ventral striatum, ventral tegmental area, and substantia nigra (pars compacta) was described when experimental animals did not receive the expected reward, that is, in extinction trials [7]. Indeed, it appears that spontaneous confabulators fail in precisely this capacity: they fail to adapt their thought and behavior to the non-occurrence of anticipated outcomes and continue to act according to activated memories that do not relate to ongoing reality [3]. A dopamine antagonist such as risperidone might reduce the tendency to maintain a currently irrelevant mental associations or expectations in an active state or an inappropriate format [3]. This interpretation also predicts that spontaneously confabulating patients with very severe storage failure, who are unable to retain at least some information in memory, may not improve under risperidone mediated inhibition of currently inappropriate memories. The patient presented here had intact storage capacity, as measured by the first run of our continuous recognition task. Although this interpretation remains speculative, the present study shows that risperidone can be useful to correct the reality confusion characterizing spontaneous confabulation. It remains to be

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seen whether this effect requires some intact memory capacity (ability to store information) and whether it depends on the precise lesion location or the stage of the disease.

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Acknowledgements: Study supported by Swiss National Science Foundation grant no. 3200B0-100152 to A.S.