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Functional Neuroanatomy of Hypnotic State

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Background: *The aim of the present study was to describe the distribution of regional cerebral blood flow during the hypnotic state (HS) in humans, using positron-emission tomography (PET) and statistical parametric mapping.*

Key Words: Cerebral blood flow, positron-emission to mography, statistical parametric mapping, hypnosis, mental imagery

Methods: *The hypnotic state relied on revivification of pleasant autobiographical memories and was compared to imaging autobiographical material in "normal alertness." A group of 9 subjects under polygraphic monitoring received six* $H_2{}^{15}O$ *infusions and was scanned in the following order: alert–HS–HS–HS with color hallucina tion–HS with color hallucination–alert. PET data were analyzed using statistical parametric mapping (SPM95).*

Results: *The group analysis showed that hypnotic state is related to the activation of a widespread, mainly left-sided, set of cortical areas involving occipital, parietal, precentral, premotor, and ventrolateral prefrontal cortices and a few right-sided regions: occipital and anterior cingulate cortices.*

Conclusions: *The pattern of activation during hypnotic state differs from those induced in normal subjects by the simple evocation of autobiographical memories. It shares many similarities with mental imagery, from which it differs by the relative deactivation of precuneus.*

Introduction

Hypnosis has been used as a therapeutic tool since mankind's early history (De Betz and Sunnen 1985). Nevertheless, its acceptance by the scientific community remains limited. Consequently, the neural correlates of hypnotic state (HS) remain poorly understood. One field where the efficacy of HS has been objectively evaluated and validated is pain control (Faymonville et al 1995).

Since 1992, more than 1350 patients underwent surgical procedures with a specific anesthetic method combining local anesthesia, conscious sedation, and hypnosis (Faymonville et al 1995, 1996, in press). This procedure was proposed instead of general anesthesia. We showed that the HS procedure significantly increased patient (and surgeon) comfort.

To better understand what happens in patients in the HS during surgery, we decided to explore the brain mechanisms underlying the HS in healthy volunteers by deter mining the distribution of regional cerebral blood flow (rCBF), taken as an index of local neuronal activity. The HS was induced in the same way as it is in patients during surgery (eye fixation, progressive muscular relaxation, and evocation of pleasant life experience). Regional cerebral perfusion was determined by positron-emission tomography (PET), with $H_2{}^{15}O$ infusions. Data were analyzed using statistical parametric mapping (SPM).

The study reported here should be considered as a first step in our approach to HS; it focuses on HS processes per se. The analgesic effects of HS are specifically explored in another experimental protocol.

Methods and Materials

Subjects' Selection

This study was approved by the Ethical Committee of the Faculty of Medicine of the University of Liège. Young healthy right-handed subjects were considered for selection, after they gave their written informed consent. All of them were people working in the operating theater, and they applied spontaneously to participate to the experiment. From a cohort of 30 screened subjects, 15 were selected because they were scored as highly hypnotizable subjects (score >8) on the Stanford scale–form C (Hilgard et al 1963). During the selection procedure, which took place several weeks before the experi mental session, subjects were asked to recall souvenirs they wanted to be used on the scanner.

PET Acquisitions

Experiment 1. Nine subjects (7 female, 2 male; mean age 30.7 years; age range 23-38) participated in the study. Before the scanning session, electrodes were put in place to monitor electroencephalogram (EEG) (C3-A2 and C4-A1), horizontal electro-oculogram (EOG), and chin electromyogram (EMG). A venous catheter was inserted under local anesthesia in a left antebrachial vein. The subject's head was stabilized by a ther moplastic face mask secured to the head-holder (Truscan imaging, MA). Earphones were adapted to the subject's head. Verbal communications were made at a distance via a microphone at all times. A transmission scan was performed to allow a measured attenuation correction. In both experiments, six emission scans were acquired. Each consisted of two frames: a 60-sec background frame and a 120-sec frame. The slow intravenous water ($H_2{}^{15}O$) infusion was begun just before the second frame to observe the head curve rising within the first 10 sec of this frame. Thirty millicuries (1110 MBq) were injected for each scan, in 10 cc saline, over a period of 60 sec. The infusion was totally automated so as not to disturb the subject during the scanning periods. Data were acquired by a Siemens CTI 951 R 16/31 scanner in 2D mode. Data were reconstructed using a Hanning filter (cutoff frequency: 0.5 cycle/pixel) and corrected for attenuation and background activity. The final in-plane image resolution was 8.7 mm full width at half maximum (FWHM) (Degueldre and Quaglia 1992).
Each subject was scanned twice in each of three conditions, under continuous polygraphic monitoring. In the first condition (I: alert state with autobiographical information), the subjects were studied while listening to sentences containing pleasant information taken from their own past. Subjects were instructed to imagine what happened to them in the described situations. The subjects were urged not to try to enter a hypnotic state. In the second condition (II: hypnotic state), the subjects were scanned after the hypnotic state was induced. Hypnotic state was considered to be present when roving eye movements were observed on oculography and if, just before the scan, the subject responded by a foot movement that he felt in HS. During the hypnotic state, subjects were invited to have revivification of pleasant life experiences. In the third condition (III: hypnosis with forced color hallucinations), while in hypnotic state, the subject was asked to focus on their preferred colors and to view settings and objects in these colors. Scan was also acquired after the subject manifested by a foot movement that he actually succeeded in attaining the targeted colors.
To avoid multiple hypnotic inductions that would have unduly lengthened the experimental procedure, the acquisitions during HS were blocked in the middle of the session. In consequence, the order of injections was I, II, II, III, III, I for all subjects. Subjects were scanned with eyes closed throughout the experimental procedure. Ambient noise was reduced to a minimum, and ambient light was dimmed. The same experimenter (MEF) spoke to the subjects in all conditions.

Experiment 2. This experiment was designed to evaluate the distribution of regional cerebral blood flow during revivification of personal memories, which served as the control situation in experiment 1.
Six subjects (4 female, 2 male; mean age 29.3 years; age range 24–39) participated in this experiment, during which we contrasted the autobiographical condition to a resting condition. In the first condition (IV: rest), subjects were scanned in a resting state and were asked to empty their mind. The second condition (V: autobiographical) exactly replicated the control condition of the first experiment. The third condition (VI) was part of a larger study on language processing and will not be discussed here. In this condition, the subjects heard the auditory stimuli presented during condition V, played backward on a tape.
The order of injection respected a Latin square design (IV, V, VI, VI, V, IV) and was counterbalanced over subjects. Subjects were scanned with eyes closed throughout the experimental procedure. Ambient noise was reduced to a minimum, and ambient light was dimmed. Data acquisition was identical to experiment 1, except that no polygraphic recording was obtained.

Data Analysis

PET data were analyzed using the statistical parametric mapping software (SPM95 version; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, U.K.) implemented in MATLAB (Mathworks Inc., Sherborn, MA). In short, data from each subject were realigned using a least square approach and the first scan as a reference (Friston et al 1995a). Following realignment, all images were transformed into a standard space (Friston et al 1995a; Talairach and Tournoux 1988) and then smoothed using a 12-mm FWHM isotropic kernel. A design matrix was specified, according to the general linear model (Friston et al 1995b). It included the global activity as confounding covariate (Friston et al 1990). The condition effects were first estimated at each and every voxel. The analysis used linear contrasts to identify the brain regions where rCBF was significantly increased (II+III—I) or decreased (I—II—III) in hypnosis as compared to normal alertness. The areas more active during hypnosis with color hallucination than during hypnosis alone (III—II) were also

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looked for. Finally, the analysis looked for areas more active while listening to autobiographical evocation than at rest (V—IV).

The resulting set of voxel value for each contrast constituted a map of the *t* statistic (SPM{*t*}). The SPM{*t*} were then trans formed to the unit normal distribution (SPM{*Z*}) and thresholded at $p < .001$ ($Z = 3.09$). The resulting foci of activation were finally characterized in terms of peak height over the entire volume analyzed, [$p(_{Z\max > u})$], which corresponds to a corrected *p* value < .05 (Friston et al 1991, 1994, 1995b).

Results

Experiment 1

All subjects readily entered the HS when HS induction was begun. They remained in the HS until the end of the fifth scan, as requested by the experimental protocol.

During the experimental session, EEG recordings did not show any sign of sleep (spindles, K complexes). During HS, the waking alpha rhythm was fragmented and replaced by periods of slower (theta) activities. Oculo grams systematically showed slow roving eye movements. EMG recordings were characterized by a decreased mus cular tone.

During HS with color hallucination, all subjects re ported having successfully obtained the desired color.

Table 1. Localization[a] and Statistical Results[b] Concerning the Local Maxima of the Brain Areas Where rCBF Is Significantly Higher or Lower in Hypnotic State than during Imaging Autobiographical Material in "Alert" State

Side	Cerebral area	BA	x	y	z	Z score	p (corrected)
Increases in HS							
Left	Occipital cortex	18	−24	−96	−4	4.30	.032
			−30	−76	0	4.71	.006
			−24	−82	0	5.05	.001
		19	−30	−68	−4	4.37	.024
			−20	−62	36	5.37	<.001
		37	−50	−56	−20	4.92	.002
Right	Occipital cortex	18	2	−78	−4	4.73	.006
			6	−70	−8	4.24	.039
Left	Inferior parietal lobule	40	−24	−48	28	5.66	<.001
			−40	−34	32	4.88	.003
Left	Precentral cortex	4	−48	−8	32	4.63	.008
		4/6	−36	−4	32	4.39	.022
		4/43	−42	−10	20	4.27	.035
			−26	−22	36	4.44	.018
Left	Prefrontal cortex	45	−28	26	8	5.45	<.001
			−24	22	16	5.16	.001
			−28	12	20	4.61	.009
Right	Anterior cingular cortex	24/32	14	32	16	4.43	.019
Right	Cerebellum		16	−52	−28	5.85	<.001
			10	−64	−12	4.96	.002
Decreases in HS							
Left	Temporal cortex	20	−56	−16	20	4.71	.006
		21	−46	0	20	4.91	.003
			−60	−34	8	4.23	.041
		38	−26	16	20	5.29	<.001
			−40	8	20	4.47	.017
		39	−46	−64	4	4.41	.021
Right	Temporal cortex	21	48	0	16	7.11	<.001
			60	−24	4	5.28	<.001
		22	56	−30	4	5.12	.001
Medial	Prefrontal cortex	8	−6	34	4	5.10	.001
			−4	26	8	4.86	.003
			−6	12	8	4.17	.050
		9	−4	50	4	4.82	.004
		10	0	50	8	4.22	.042
Right	Premotor cortex	6	42	2	4	5.64	<.001
Medial	Precuneus	7	−2	−56	4	5.70	<.001
Right	Cerebellum		18	−82	−28	4.35	.026

[a]Coordinates are defined in the stereotactic space of Talairach, relative to anterior commissure. x represents the lateral distance from midline (positive = right); y is the anteroposterior distance from anterior commissure (positive = anterior); z represents the rostrocaudal distance from the bicommissural plane (positive = rostral).

[b]The areas are significant at a threshold of p = .001, by reference to unit normal distribution (Z = 3.09), and at a threshold of corrected p < .05 (corrected p, the probability that the regional rCBF variation could have occurred by chance over the entire volume analyzed).

Significant increases in rCBF during hypnosis (condi tions II and III) as compared to normal alertness (condition I) were observed in four regions (Table 1, Figure 1A). The largest excursion set was left-sided and involved extrastriate visual cortex [Brodmann's area (BA) 18, 19, 37], inferior parietal lobule (BA 40), precentral and adjacent premotor (BA 6) cortex, and the depth of ventrolateral prefrontal cortex (BA 45), close to the insular cortex. The second area was right-sided and involved deep cerebellar nuclei and prestriate cortex (BA 18). The two last areas are the right anterior cingulate cortex (BA 24/32) and left occipitotemporal cortex (BA 37).
Significant decreases in rCBF during hypnosis as compared to normal alertness (Table 1, Figure 1B) were observed in left temporal cortex (BA 20, 21, 38, 39), right temporal cortex (BA 21, 22), medial prefrontal cortex (BA 8, 9, 10), posterior cingulate (BA 39) and adjacent precuneus (BA 7), right premotor cortex (BA 6/8), and right cerebellar hemisphere. No significant rCBF variations were detected between hypno sis with and without forced color hallucination.
The comparison of conditions III and II (effects of color hallucinations during HS) provided no significant results.

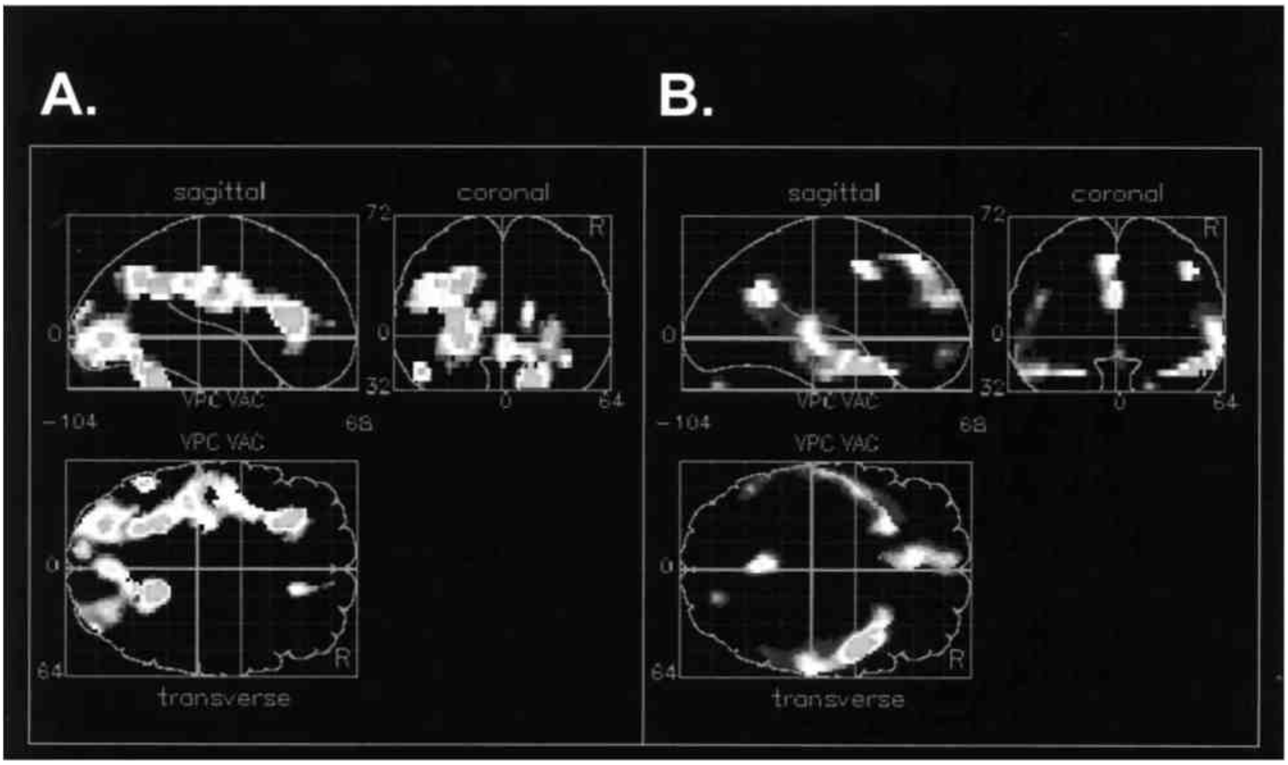

*Figure 1. Projections in the Talairach's stereotactic space of brain areas where rCBF is significantly increased **(A)** or decreased **(B)** during hypnosis, as compared to normal alertness with autobiographical information. Functional PET results are displayed at threshold of Z = 3.09 (p < .001). VPA and VPC identify anterior and posterior commissural planes, respectively.*

Experiment 2
Significant increases in rCBF (Table 2) during the autobiographical condition (condition V) as compared to rest (condition IV) were observed bilaterally, in temporal poles (BA 38), superior (BA 42) and middle (BA 21 and 22) temporal gyrus, and a region located near the basal forebrain. On the left side, significant increases were observed in the left entorhinal cortex, and in the premotor cortex (BA 6).

Discussion

Assessment of the Hypnotic State

The critical issue in this experiment was that the hypnotic state was internally generated, and that no output was required from our subjects. In consequence, we had to resort to all sorts of precautions to ascertain, as objectively as possible, the presence of the hypnotic state during scanning. First, the subject's behavior and clinical appearance was identical to that routinely observed in patients undergoing surgical interventions or burn debridement under hypnosis (Faymonville et al 1995, 1996, in press). Second, oculograms showed slow eye movements, inter mingled with ocular saccades. It should be emphasized that slow roving eye movements cannot be willingly mimicked (Plum and Posner 1980). Their presence rules out any simulated state. Third, if polygraphic recordings sometimes showed a fragmentation of a rhythm and the outbreak of slow (theta) rhythm bursts during hypnosis, overt signs of sleep (K complexes or spindles) never occurred. Fourth, the subjects were requested, just before each scan, to manifest they actually felt themselves to be in a hypnotic state. They were also interviewed afterwards about their hypnotic experience. All subjects admitted that they readily fell into a hypnotic state at the induction and remained in this state as long as requested. They usually reported having experienced vivid, detailed, and colorful revivifications of pleasant memories, having actually mentally reenacted them.

Each of these points, taken in isolation, does not prove there was a hypnotic state in our subjects, but together they form a body of arguments that, by their co-occurrence, strongly suggest that this was the case.

Comparison with Previous Neuroimaging Data in HS

Only a handful of neuroimaging studies using PET or single photon emission computed tomography (SPECT) have explored the hypnotic state. Their results did not succeed in sketching a consistent metabolic pattern for the HS.

Table 2. Localization and Statistical Results Concerning the Local Maxima of the Brain Areas Where rCBF Significantly Increases during Evocation of Autobiographical Memories, as Compared to "Rest"

Side	Cerebral area	BA	x	y	z	Z score	p (corrected)
Left	Temporal cortex	21	−56	−26	0	6.34	<.001
		22	−58	−40	4	5.01	.002
			−50	−2	−4	4.85	.003
		38	−46	6	−12	4.50	.014
		42	−38	−28	8	4.61	.009
Right	Temporal cortex	21	52	−10	−4	5.25	.001
			48	−2	−12	4.96	.002
		22	52	−28	4	7.17	<.001
		38	40	12	−12	5.30	<.001
Left	Premotor cortex	6	−38	−2	44	4.87	.003
Left	Mesiotemporal	28	−22	10	−20	4.41	.021
Left	Basal forebrain		−10	2	−8	4.66	.007
Right	Basal forebrain		22	4	−8	5.39	<.001

Coordinates and statistical results determined as in Table 1.

During hypnosis, increases in rCBF of various cerebral regions (right frontal, orbitofrontal, temporal, motor, and somatosensory areas) were reported in SPECT studies (Crawford et al 1993; Diehl et al 1989; Halama 1989; Meyer et al 1989). Using PET, it was observed that the glucose metabolism was decreased in occipital regions and was increased in sensorimotor areas during HS (Grond et al 1995).

The diversity of results is in part due to the experimental conditions that explored various aspects of hypnosis (mainly hypnotic analgesia and cataleptic hypnosis). Fur thermore, in many of these studies, the spatial resolution of the technique was not sufficient to yield a detailed map of the HS metabolic pattern.

rCBF Distribution during HS

The choice of the control task was a difficult one for, a priori, no cerebral state was close to the HS. Because the induction and maintenance of HS relies on revivification of pleasant autobiographical memories, the closest situation was the evocation of autobiographical information, in the absence of the hypnotic state. To better understand the comparisons made for HS, we set up experiment 2, investigating the control condition of the first experiment. The results showed that listening to autobiographical material activates the anterior part of both temporal lobes, basal forebrain structures, and some left mesiotemporal areas. This metabolic pattern is in excellent agreement with a recent PET study of autobiographical memory (Fink et al 1996).

In contrast, during HS, a vast activation was observed that involved occipital, parietal, precentral, prefrontal, and cingulate cortices. The metabolic distributions due to hypnotic state and to evocation of autobiographical information did not overlap. These results show that HS relies on cerebral processes different from simple evocation of episodic memory and suggest that HS is related to the activation of sensory and motor cortical areas, as during perceptions or motor acts, but without actual external inputs or outputs. In this respect, hypnosis is reminiscent of mental imagery (Kosslyn 1993). The imagery content in HS was polymodal. Although subjects predominantly reported visual impressions, somesthetic and olfactory perceptions were also mentioned. A lot of

actions also appeared in the hypnotic experience of most of our subjects. In contrast, none of the subjects reported auditory imagery. When sounds were mentioned, they came from the actual experimental environment (mainly, the experimenter's voice).
The visual mental imagery might take into account the activation of a set of occipital areas. The activation of early visual areas (BA 18, occipital pole) has been proposed as a visual buffer organizing visual information (Kosslyn et al 1993). Ventral regions (lingual and fusiform gyrus, BA 37) would reflect the recognition and discrimination of face and object features (Haxby et al 1991; Sergent et al 1992), whereas more dorsal activation (BA 39 and 40) would be related to the spatial organization of visual imagery (Kosslyn et al 1996). The left-sided pre dominance of the activation has previously been reported in visual mental imagery. Left hemisphere would be more able to generate and arrange parts of mental images (Farah 1984), although both hemispheres have specific imagery capacities (Kosslyn et al 1993). More anteriorly, the activation of precentral and premotor cortices is similar to that observed during motor imagery (Decety et al 1994), which could also have participated in the parietal activation (Stephan et al 1995). The activation of ventrolateral prefrontal cortex has also been observed in mental imagery tasks (Kosslyn et al 1996) and would be involved in the programming of the building up of the mental image or in the maintenance of image in memory. In this respect, the left-sided lateralization is not easily explained. We do not feel that prefrontal activation could reflect subvocal subjects' vocalization, because orofacial movements are usually less frequent in hypnosis. Finally a right-sided activation of anterior cingulate cortex would probably reflect the attentional effort necessary for the subject to internally generate mental imagery (Devinsky et al 1995; Posner and Petersen 1990).
Some cortical areas are significantly less active during hypnosis that during the alert state. These temporal deactivations might simply emphasize that autobiographical evocation is, in contrast to HS, characterized by a prominent activation of anterior temporal lobe structures (experiment 2 and Fink et al 1996). Alternatively, the deactivation of anterior parts of both temporal lobes could also indicate that subjects did not resort to auditory mental imagery, which is known to activate temporal areas (Zatorre et al 1996). It could also be explained by the experimental conditions. The examiner's speech rate was lower during the hypnosis than during alert conditions. This parameter is known to influence the activity of left superior temporal cortex (Price et al 1992). Likewise, processing of pitch (which was lower and more monotonous during HS) depends on right hemisphere structures (Zatorre et al 1992; Zatorre and Samson 1991).
The deactivation of precuneus has been reported during visual discrimination tasks, when visual stimulus is physically present (Shulman et al 1996). In contrast, precuneus is usually activated in tasks requiring mental imagery (Kosslyn et al 1996), long-term memory (Grasby et al 1993), and visual attention (Corbetta et al 1993). The deactivation of precuneus is certainly an important metabolic feature distinguishing hypnotic state from alert visual mental imagery.
The mesial frontal deactivation remains speculative, as the function of this part of the prefrontal cortex remains fragmentary. Such deactivation has been reported in several tasks, such as visual discrimination (Shulman et al 1996) and mental arithmetics (Ghatan et al 1996). It would reflect the interruption of tasks going on during alert condition, irrelevant to the HS, such as unconstrained monitoring of environment, emotional state, or thought processes.

Comparison with Other Internally Generated Mental Experiences

Hypnotic state should be distinguished from other types of internally generated, polymodal perceptuomotor experiences, the functional anatomy of which has recently been
approached with PET: dreams during REM sleep in normal subjects (Maquet et al 1996), and hallucinations in schizophrenic patients (Silbersweig et al 1995).
In the present study, no subjects presented polygraphic evidence of slow sleep (sleep spindles, K complexes, or large-amplitude slow waves) or REM sleep (especially complete atonia). The distribution of regional cerebral blood flow during HS is mainly cortical and does not seem to activate the pons, the thalami, and amygdaloid complexes, in contrast to what has been observed in REM sleep with dreaming (Maquet et al 1996).
Likewise, HS differs from the schizophrenic hallucinations (estimated on a group of patients) by the absence of subcortical and paralimbic activation and by the activation of lateral prefrontal cortex (Silbersweig et al 1995).

Conclusions

Taken together, these results suggest that, in our experimental conditions, HS is a particular cerebral waking state where the subject, seemingly somnolent, experiences a vivid, multimodal, coherent, memory-based mental imagery that invades and fills the subject's consciousness.

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