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BULLETIN N° 211
ACADÉMIE EUROPEENNE INTERDISCIPLINAIRE DES SCIENCES
INTERDISCIPLINARY EUROPEAN ACADEMY OF SCIENCES

Lundi 9 janvier 2017:
à 17 h à la Maison de l'AX, 5 rue Descartes 75005 PARIS

Conférence du Dr Stein SILVA
MCU / PH Service de Réanimation / INSERM U825
CHU Purpan / Toulouse
" Apparition de la conscience à partir du coma: état de la science"

Notre Prochaine séance aura lieu le lundi 6 février 2017 à 17h
5 rue Descartes 75005 PARIS
Elle aura pour thème

Conférence du Pr Alberto OLIVEIRO
Pr Emérite Psychobiologie / Faculté des Sciences / La Sapienza/Rome
" *La vie cachée du cerveau* "

Académie Européenne Interdisciplinaire des Sciences
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ACADÉMIE EUROPÉENNE INTERDISCIPLINAIRE DES SCIENCES
INTERDISCIPLINARY EUROPEAN ACADEMY OF SCIENCES

janvier 2017

N°211

TABLE DES MATIERES

Prochaine séance : lundi 6 février 2017

Conférence du Pr Alberto OLIVEIRO
Pr Emérite Psychobiologie / Faculté des Sciences / La Sapienza/Rome
" *La vie cachée du cerveau* "

ACADEMIE EUROPEENNE INTERDISCIPLINAIRE DES SCIENCES
INTERDISCIPLINARY EUROPEAN ACADEMY OF SCIENCES

5 rue Descartes 75005 PARIS

Séance du Lundi 9 janvier 2017 /Maison de l'AX 17h

La séance est ouverte à 17h **sous la Présidence de Victor MASTRANGELO** et en la présence de nos Collègues Gilbert BELAUBRE, Jean-Louis BOBIN, Alain CARDON, Juan-Carlos CHACHQUES, Gilles COHEN-TANNOUDJI, Jean-Felix DURASTANTI, Claude ELBAZ, Michel GONDRAN, Irène HERPE-LITWIN, Gérard LEVY, PASSINI Marie-Françoise, Jacques PRINTZ, Jean SCHMETS , Alain STAHL, Jean-Pierre TREUIL .

Etaient excusés :François BEGON, Jean-Pierre BESSIS, Bruno BLONDEL, Michel CABANAC, Alain CORDIER , Daniel COURGEAU, Ernesto DI MAURO, Françoise DUTHEIL, Vincent FLEURY, Robert FRANCK, Jean -Pierre FRANCOISE, Jacques HENRI-ROBERT, Dominique LAMBERT, Valérie LEFEVRE-SEGUIN, Antoine LONG, Pierre MARCHAIS, Claude MAURY, Anastassios METAXAS, Jacques NIO, Edith PERRIER, Pierre PESQUIES, Michel SPIRO, Jean VERDETTI.

I. Présentation de notre conférencier Stein SILVA par notre Président Victor MASTRANGELO

Voici le CV résumé de notre conférencier:

Titulaire d'une Thèse en Médecine avec prix du Jury de la Faculté de Nancy il détient également les diplômes suivants :

- Master 2 Recherche (« Neuropsychologie » Toulouse,).
- Certificat MSBM (« Physiologie neurosensorielle et neurobiologie des comportements » Montpellier,).
- Certificat MSBM (« Neurobiologie appliquée » Montpellier).
- DES d'Anesthésie Réanimation (Nancy, Médaille d'or).
- DESC de Réanimation Médicale (Toulouse, Médaille d'or)
- **Thèse de Science («Corrélats neuronaux de la conscience», UPS, ED CLESCO, Toulouse).**
- **Habilitation à Diriger des Recherches** (HDR) («Utilisation de l'imagerie multimodale dans la compréhension et la prise en charge des défaillances d'organes sévères», UPS, ED CLESCO, Toulouse).

- Traitement Statistiques Paramétrique (INSERM, Paris).
- Techniques d'IRM appliquées (School of MRI, Paris).

Il a également effectué un séjour postdoctoral au Wolfson Brain Imaging Center, Cambridge University, UK (Pr DK Menon).

Il exerce actuellement les fonctions de Maître de Conférence des Universités - Praticien Hospitalier (MCU-PH) à l'hôpital Purpan de Toulouse . Auparavant il y a exercé les fonctions d'Assistant-Chef de Clinique puis de Praticien Hospitalier .

Il travaille en collaboration avec les principaux organismes suivants:

- INSERM: 825 (Toulouse, France)
- CNRS: CerCo (Bron, France).
- Research Memory Center (Laussane, Suisse)

- Wolfson Brain Imaging Center (Cambridge, UK).
- Brain Mapping Center (UCLA, Los Angeles, USA)
- ITAB, Brain Imaging and Cognition (Rome, Italie).
- Instituto de Ciencias Cognitivas (Buenos Aires, Argentina).

Il est également auteur ou co-auteur de publications scientifiques récentes dans des revues à comité de lecture dont les suivantes dédiées au cerveau :

1. Silva S, et al. Wakefulness and loss of awareness: brain and brainstem interaction in the vegetative state. *Neurology* 2010;74:313---20.
2. Silva S, et al. Temporal analysis of regional anaesthesia-induced sensorimotor dysfunction: a model for understanding phantom limb.*Br J Anaesth* 2010; 105: 208---13.
3. Silva S, et al. Impaired visual hand recognition following regional anesthesia of the upper limb: implication of acute brain plasticity. *Anesthesiology* 2011.
4. Schmidt E, Silva S et al. Cerebral hemodynamic changes induced by lumbar puncture in good grade subarachnoid hemorrhage. *Cerebrovasc Dis*, 2012
5. Silva S. et al., Disruption of posteromedial large-scale neural communication predicts recovery from coma.*Neurology*, 2015.

II. Conférence de Stein SILVA

Résumé en français de la présentation de Stein SILVA:

Apparition de la conscience à partir du coma: état de la science

Le concept de conscience continue à rendre toute tentative de définition problématique et à échapper à l'effort philosophique et scientifique de formuler un schéma testable de l'expérience consciente. Avoir subi une blessure cérébrale sévère cause une perte de conscience ce qui fournit un modèle de lésion à partir duquel on peut tirer des idées-clé concernant l'apparition de la conscience. En milieu clinique le spécialiste est confronté au problème de la détection et du suivi de la récupération de la conscience chez des patients ayant subi une blessure du cerveau et qui sont dans un premier temps dans l'incapacité de communiquer verbalement ou gestuellement.

Les découvertes en neuro-imagerie et en électrophysiologie ont suscité l'attention des scientifiques et des cliniciens car de plus en plus d'éléments tendent à montrer qu'ils peuvent détecter des processus actifs de cognition et identifier les changements structurels et fonctionnels du cerveau en relation avec une perte de conscience pathologique. Nous allons fournir un aperçu de l'état de la science dans ce domaine en nous concentrant sur les retombées cliniques potentielles dans le domaine du traitement des patients comateux et sur les problèmes éthiques propres à cette population.

Un compte-rendu détaillé sera prochainement disponible sur le site de l'AEIS , http://www.science-inter.com

Annonces

I. **Quelques ouvrages papiers relatifs au colloque de 2014 " Systèmes stellaires et planétaires- Conditions d'apparition de la Vie" -**

- Prix de l'ouvrage :25€ .
- Pour toute commande s'adresser à :

Irène HERPE-LITWIN Secrétaire générale AEIS
39 rue Michel Ange 75016 PARIS
06 07 73 69 75
irene.herpe@science-inter.com

Documents

- p. 07 Notre collègue de Nancy Franck COSSON qui a fait une conférence sur "*La Conscience animale* " nous en a fait parvenir une synthèse .
- P. 09 Notre Collègue Michel CABANAC de l'Université Laval de Québec nous a fait parvenir un de ses articles publié sur http://www.elsevier.com/locate/bbr correspondant à l'ouvrage Behavioural Brain Research 198 (2009) 267–272 , intitulé "*The Emergence of Consciousness in Philogeny*"
- P.15 Un article du Monde abonné du 9 janvier 2017 de David Larousserie dédié à "*La Révolution des neurones artificiels"*

Pour préparer sa conférence le Pr Alberto OLIVEIRO nous a communiqué des articles:

- p.20 tiré de http://www.pnas.org/content/107/17/7945.full un article intitulé " *Ventral striatal plasticity and spatial memory*"
- p. 26 tiré de http://www.oliverio.it/ao/creativity.pdf un article intitulé " Brain and Creativity"

-Intervention de Franck Cosson, AEIS Section de Nancy-

« LA CONSCIENCE ANIMALE »

L'interrogation sur la conscience animale rencontre un écueil d'ordre épistémologique et méthodologique qui s'explique par un héritage philosophique et culturel qui réduit *a priori* toute conscience au pouvoir de saisir une identité abstraite sous la forme *d'un Je méta - biologique transcendant le corps – propre et l'ensemble des fonctions vitales y compris le cerveau.* Dans une perspective philosophique ouverte aux apports de la science des animaux - de la physiologie au fonctionnement cérébral et de l'éthologie à l'écologie et aux sciences de l'évolution - deux approches complémentaires sont développées dans ce travail qui se veut interrogatif et prospectif :

1) Une approche intégratrice et éthologique fondée sur une analyse de type phénoménologique

Elle interroge l'idée d'une synthèse d'états organiques multiples différents mais « intégrés » au fonctionnement unifié de l'animal, laissant émerger la possibilité *d'une auto – affectation globale* permettant de proposer l'hypothèse que certains animaux disposeraient d'une notion de ce qu'ils éprouvent et de ce qu'ils sont *comme sujets corporels affectés. Cette notion* correspondrait à une forme émergente de connaissance de son être sensible voire à une forme de connaissance de soi c'est – à - dire à l'émergence d'une connaissance unifié du corps – propre qui pourrrait s'avérer fort proche d'un acte de conscience.

La conscience animale pourrait alors être indissociable de plans d'organisation de plus en plus complexes connectés au système cérébral et correspondre à l'émergence de niveaux d'intégration faisant l'objet d'une saisie et d'une mise en forme de la part de l'organisme en acte gagnant ainsi en autonomie comportementale et vitale. La difficulté consiste à repérer un franchissement de seuil impliquant de passer d'un niveau inconscient (automaticité des chaînes de réaction) au niveau de l'émergence d'une auto – affectation pré – consciente qui permette déjà à l'animal de se distinguer en tant qu'être ou sujet par ce qu'il éprouve ou ce qu'il connaît de lui – même comme corps en acte motivé ou « intentionné » préfigurant ainsi la propriété de réflexivité caractéristique essentielle de toute consceince. Ce seuil d'émergence conférerait une cohérence comportementale centralisée et unifiée permettant à l'animal d'accéder à des niveaux d'existence plus complexes et plus indéterminés laissant émerger le thème du choix et de la liberté, l'être animé échappant ainsi à un strict déterminisme « mécanique » et naturel.

Sur le plan éthologique et évolutif enfin si l'animal ne dispose pas d'une fonction cognitive permettant l'accès unifié à la multiplicité de ses états, la question se pose de savoir comment il pourrait survivre dans des circonstance qui exigent des réactions comportementales efficaces, motivées et autonomes. La conscience pourrait bien devenir de ce point de vue un postulat nécessaire à l'intelligibilité des comportements supérieurs que nous avons en commun avec maints animaux et constituer l'un des fondement épistémologique de la recherche en éthologie intégrant alors l'animal humain dans une perspective croisée.

2) Une approche « croisée » de type anthropozoologique

Elle s'interroge sur la possibilité pour l'homme d'entretenir avec certains animaux des formes de compréhensions mutuelles fondées sur des phénomènes d'empathies interspécifiques.

L'investigation porte sur la possibilité pour l'animal d'accéder à la compréhension de situations ou d'événements ayant, au départ, une signification humaine. Cette compréhension lui permettrait d'accéder à des formes nouvelles d'intelligence de soi – même, des autres êtres impliqués dans l'interaction et de situations plus ouvertes et plus complexes que celles auxquelles il pourrait être naturellement confronté, ouvrant à l'investigation sur la conscience un questionnement sur l'existence de mondes communs ou partagés entre l'espèce humaine et d'autres espèces notamment domestiquées.

Franck COSSON
Agrégé et Docteur en philosophie, qualifié au fonctions de Maître de conférence (Philosophie).
S'est intéressé à la zoologie et à l'écologie avant d'entreprendre des études de philosophie.
A publié : *L'animal médiateur de l'humain* (2007. Revue internationale de psychosociologie)
Animalité et humanité. La frontière croisée (editions Ovadia, Novembre 2016).
Ouvrage en préparation : *Phénoménologie des formes animées.*

Behavioural Brain Research 198 (2009) 267–272

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Review

The emergence of consciousness in phylogeny

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ABSTRACT

The brains of animals show chemical, anatomical, and functional differences, such as dopamine production and structure of sleep, between Amniota and older groups. In addition, play behavior, capacity to acquire taste aversion, sensory pleasure in decision making, and expression of emotional tachycardia and fever started also to be displayed by Amniota, suggesting that the brain may have began to work differently in early Amniota than in Lissamphibia and earlier vertebrates. Thus we propose that emotion, and more broadly speaking consciousness, emerged in the evolutionary line among the early Amniota. We also propose that consciousness is characterized by a common mental pathway that uses pleasure, or its counterpart displeasure, as a means to optimize behavior.

Contents

1. Introduction

What is consciousness? Bering and Borklund [1] define it as "a higher-order cognitive system enabling access to intentional state." That new property may have emerged because of the increasing complexity of life in a terrestrial environment [2]. In this new adaptive landscape, existence required more and more stimulus–response pathways; eventually, a point was reached where it became more efficient, in terms of speed and flexibility, to route all decision making through a single mental space. Within this space, different possible responses could be simply matched according to the criterium of maximal pleasure [3]. With Rial et al. [4] we may acknowledge that "attaining a positive proof of adaptiveness is extremely difficult". However, it seems obvious that such a simplified process gave a survival advantage to those animals that

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acquired it, and pleasure/consciousness was maintained and transmitted to us.

Based on experimental as well as theoretical arguments Cabanac proposed previously that it was sensory pleasure/displeasure that made consciousness so useful that such emerging new property was selected and maintained through natural selection [3,5]; thus conscious animals did not have anymore to accumulate behavioral reflexes to produce useful responses but could just maximize sensory pleasure. In the following we shall define it as an abstract private model of reality, with four dimensions: quality, intensity, hedonicity, and duration.

The first dimension of sensation is qualitative and describes the nature of the stimulus or the mental object. A blue color, a sweet taste, a remembrance, etc., describe the nature of the mental experience. The second dimension of sensation is quantitative and describes the intensity of the stimulus, a bright color, a loud noise, etc. The third dimension is affective (hedonic). It may be difficult to disentangle affectivity from intensity because they most often covary together. Yet, this can be done (e.g., in the cases of sensation). All sensations are either unpleasant, indifferent or pleasant. Incidentally, this includes pain, a sensation most often unpleasant but sometimes indifferent or even, but rarely, pleasant. Sensory pleasure possesses several characteristics: pleasure is contingent, pleasure is the sign of a useful stimulus, pleasure is transient, pleasure motivates behavior. The fourth dimension of sensation is duration, which describes the extent of time a stimulus is present.

These dimensions allow the human mind for example to call up a broad range of recollected, apprehended, or even totally imagined realities. The result is increasingly complex mental activity: thoughts, feelings, and emotions assume a life of their own within a space that is relatively independent of simple stimulus–response pathways. When this space includes a representation of oneself and how this self interacts with reality, we have the beginnings of self-consciousness.

Consciousness was long considered a human privilege, all other animals being merely machine-like beings [6]. This view was challenged when Darwin [7] pointed-out that other mammals could express emotion. The question then faded into the background, largely because of the excesses of psychoanalysis and the efforts of the behaviorist school to make behavior the only object of study, to the exclusion of *underlying* thought processes [8]. Recently, there has been renewal of interest in animal consciousness [9,10] and a growing acceptance that humans are not the only thinkers. Indeed, if we accept indirect evidence for the existence of human consciousness in other people, i.e., from the verbal and behavioral signs that they provide, why should similar indirect evidence be rejected when it comes to animals? Although less direct than that provided through verbal communication, such evidence is available [9–13].

Yet, one must be prudent and always remain aware that the evidence is always indirect [14]. For example many fishes display complex behaviors such as cheating, altruism, species recognition, individual recognition, cleaning symbiosis [15] that we would be tempted to consider signs of consciousness, but can be explained on the basis of simple reflexes. Also, the complex foraging and social communication behavior of bees is often considered intelligent and 'conscious;' however, Gould and Grant-Gould [16] have shown that it was purely reflexive, in the same way as a computer can be artificially intelligent.

If we exclude self-consciousness – a human property[1] – from the private model of reality that consciousness is, we may ask the question of which animals are conscious? And which are not? At what point in evolution did nervous systems cease to operate only on a reflexive basis [17,18]? Before apes? Mammals? Vertebrates? In the following we will argue that the transition occurred between Lissamphibia and Amniota, i.e., among the amniotes, common ancestors of present-day Mammalia, Chelonia, Lepidosauria, and Archosauria.

This argument has support from the two lines of evidence developed below: anatomy and behavior.

2. Anatomy

2.1. Brain volume and structure

Because consciousness places a high demand on brain capacity, it should vary with brain size. For interspecies comparisons, brain size is best measured by the ratio of brain mass to body mass, i.e., the encephalization quotient (EQ), which corrects for differences in overall body size. EQ shows a clear-cut difference between two categories of vertebrates: ectotherms on the one hand, and endotherms on the other. The latter are warm-blooded tachymetabolic animals and have brains that are about 10 times larger than those of cold-blooded bradymetabolic vertebrates with the same body mass. In ectothermic vertebrates, the brain has the same general structure with five vesicles at the cephalic end of a neural tube. In most Lissanphibia, the telencephalon retains the structure of a simple embryonic vesicle. In Lepidosauria, we see a major change with the appearance of a new structure: the cortex (Fig. 1a). Not that the cortex should necessarily be accepted as the locus of consciousness (see Ref. [19]) but this new structure shows that complexity rose qualitatively between frogs and lizards. This anatomical difference coexists with a histological one in dopamine production.

2.2. Neurotransmitters

Brain dopamine production differs so much between Amphibia and Lepidosauria that it reaches the level of a qualitative difference (Fig. 1b) [20]. Although there is some doubt about the exclusive role of dopamine in hedonic experience, the difference remains significant given its likely involvement in mammals' hedonic experience, i.e., a conscious process [21–23].

Thus, although the coefficient of encephalization may be similar in Amphibia and lower Sauropsides, neuronal signaling has undergone a substantial qualitative change in the latter. This change is paralleled by behavioral and sensorial differences.

3. Behavioral signs of consciousness

3.1. Emotion

Handling a mammal or a bird produces tachycardia and fever [24–28], the same physiological responses of humans when they experience an emotion. Such responses are produced in Lepidosauria [27,29–31] but not in Amphibia [32] or in Teleostea [31,33] (Figs. 2 and 3).

3.2. Sensory pleasure

Rats display different facial and gestural responses when different stimuli are injected into their mouths [34–39]. These motor patterns resemble the ones that humans display when feeling pleasure or displeasure in response to the same stimuli. Similar evidence of sensory pleasure has been obtained from rats in response to temperature stimuli and temperature rewards in the absence of shivering [40]. Taste stimuli likewise induce pleasure in birds, as evidenced by a verbal response [41].

When mammals suffer nausea or diarrhea in the hours following first contact with a new food, they develop an aversion to the taste

[1] And possibly of some apes.

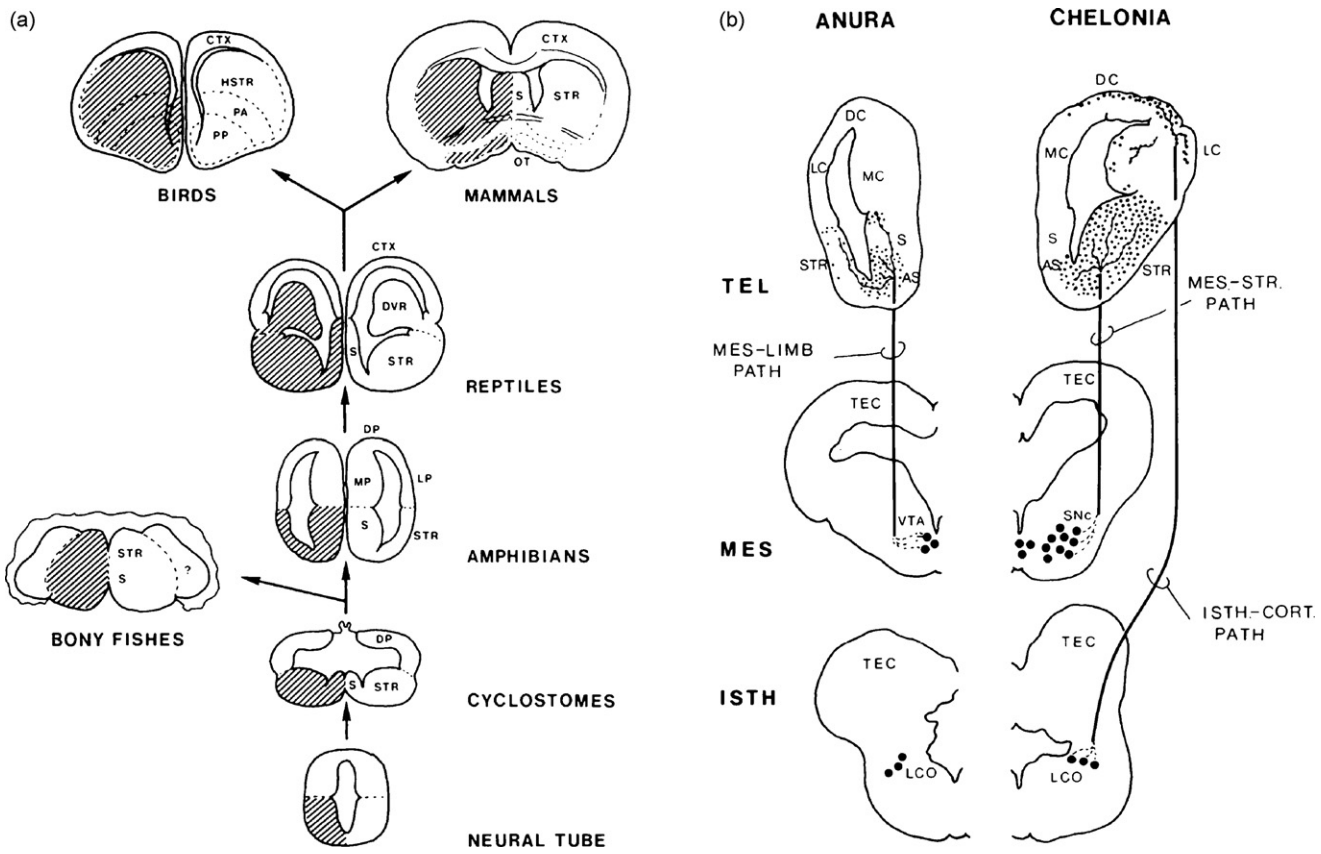

Fig. 1. From [20] anatomical evolution of the cephalic end of the neuraxis. (a) Gross anatomy: the cross-sections show that the cortex, which takes up so much of the mammalian brain, first appeared in Amniotes. Before Amniotes, the neuraxis was a relatively simple tube. (b) Shows the telencephalon and the difference in density of dopamine receptors between an amphibian (frog) on the left and a chelonian (turtle) on the right.

stimulus. Such "taste aversion learning" exists also in humans, who will describe an initially pleasant taste as now unpleasant if it has been associated with indigestion [42]. We investigated this associative learning in lizards and amphibians, both Anoura and Urodeles, by first presenting a new food and then giving intra-peritoneal injections of lithium chloride, which is known to produce nausea in mammals. When subsequently shown the same food item, the lizards avoided it if previously injected with lithium chloride, but the amphibians did not. In control sessions, intra-peritoneal saline injections produced no taste aversion learning in the lizards [43].

Because taste aversion learning in mammals is a conscious experience of what is pleasant and what is not, it is likely that Lepidosauria but not Amphibia can experience pleasure (Fig. 4).

3.3. Pleasure and decision making

In humans, conscious hedonic experience, i.e., pleasure, is the common currency that allows motivations to talk to each other. Thus, pleasure maximization provides a shortcut for making decisions without thinking them through rationally [44]. Other mammals and lizards show evidence of this mechanism: if forced to choose between avoidance of cold and hunger, lizards will maintain food intake by going out into the cold for shorter and more frequent periods [45]. But when the choice is between cold avoidance and consumption of tasty but unnecessary food (as judged from their good health and indefinite survival in the laboratory), they will go out into the cold less often and eventually give up, thus showing that the motivation is pleasure and not need (Balaskó

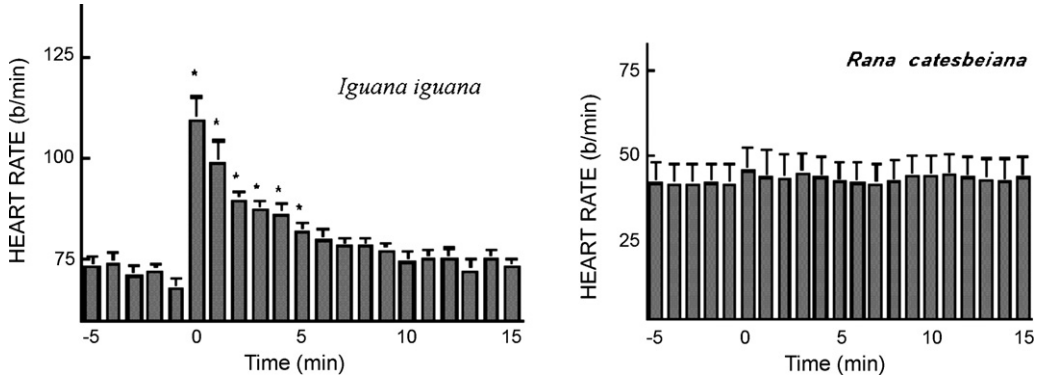

Fig. 2. Mean heart rates, over several sessions, of a lizard (left) and a frog (right) while being gently handled for 1 min at time 0. Emotional tachycardia was present in the Squamate but not in the Amphibian [31].

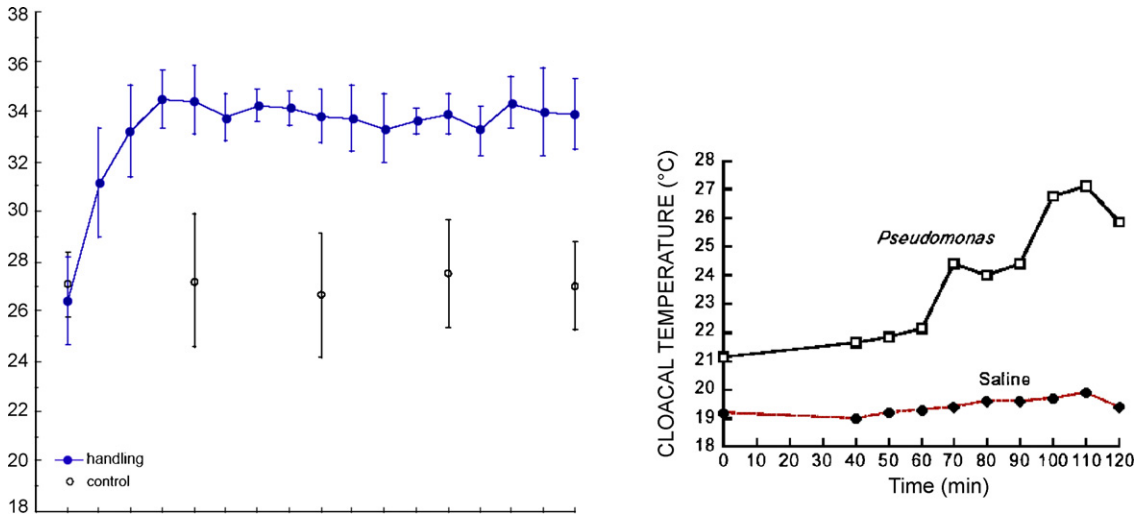

Fig. 3. Behavioral fever in a lizard (left) and a frog (right). In the lizard the fever (continuous line) was produced simply by repeated gentle handling to record cloacal temperature. The separate dots, below, give the lizard's normal temperature at the same time of day when not handled [29]. (right) No such association is present in the amphibians. Injection with pyrogens produced fever, but subsequent injection with saline caused no temperature change [32].

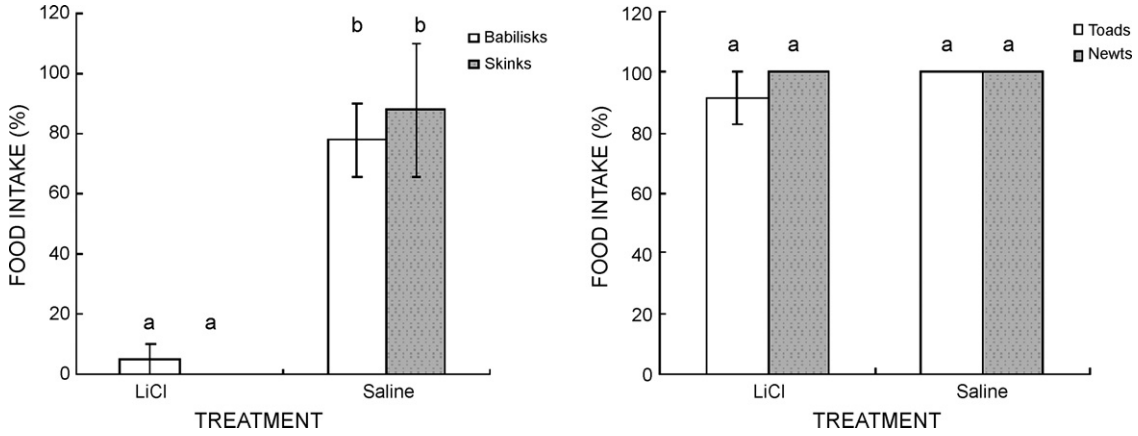

Fig. 4. Taste aversion learning in Lepidosauria (*Basiliscus vitattus*, *B. basiliscus*, *Eumeces schneideri*, *Mabuya multifasciata*) (left) but not in Amphibia (*Bufo paracnemis*, *Pachytriton breviceps* right). Left: pooled results from all species of lizards expressed in % of the food intake before treatment. LiCl columns: intake of novel food 1 week after first intake of it followed with i.p. injection of LiCl (0.15 M, 190 mg/kg). LiCl reduced intake of the novel food with which it was paired, but intake of normal food remained unaffected (102.5%, $P = 0.92$, not shown in the figure). This difference in response points to the presence of taste aversion learning. Injection of isotonic saline had no significant effect. Right: pooled results from all amphibians expressed in % of food intake before treatment. Left-hand columns: intake of novel food after i.p. injection of LiCl (0.15 M, 190 mg/kg). LiCl had no significant effect ($P > 0.10$). This similarity of response in Amphibia points to an absence of taste aversion learning. Injection of isotonic saline had no significant effect. Columns marked by the same letters are not significantly different. Those marked with different letters are significantly different ($P < 0.01$) [43].

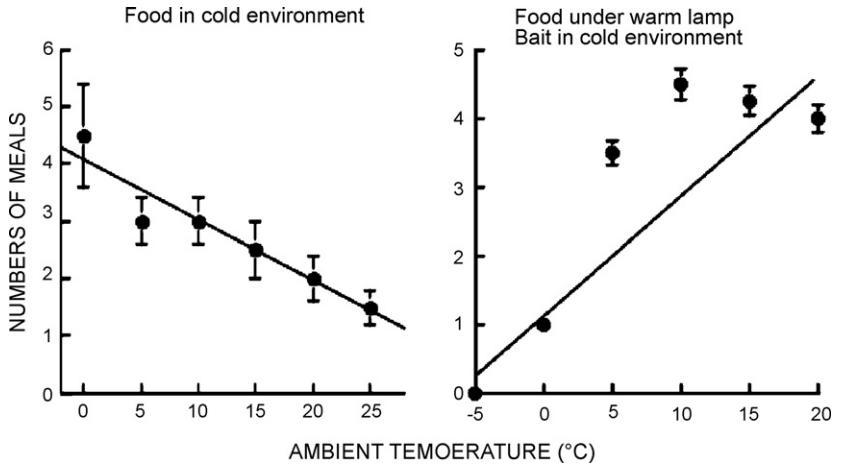

Fig. 5. Lizard food intake as a function of ambient temperature in the climatic chamber (*y*-axis: number of trips to food; *x*-axis: ambient temperature). Lizards were placed in a terrarium with an infrared lamp at one end and food at the other. Left (*Tupinambis teguixin*): when there was no food in the warm corner, they ventured into the cold to feed but did not stay long; they returned to heat themselves when their core temperature dropped. As ambient temperature fell, they made more trips to the food and back [45]. Right (*Iguana iguana*): same experiment, except that tasty food (fresh lettuce) was available at the far end while less tasty food was available under the lamp. As ambient temperature fell, the lizards made fewer trips to the far end and back. The tastiness of the food was balanced against the unpleasantness of the cold [46].

and Cabanac [48]) (Fig. 5). They behave like mammals in similar situations [46–48].

3.4. Sleep, play, and detour behavior

Mammals are awakened via the cortex whereas lepidosauria retain a simpler system controlled by brainstem neural mechanisms [49]. This older system persists in mammals but was transformed into slow wave sleep when the cortex was developed. No sleep/wake system exists in amphibians.

Burghardt [50] defined play as an "incompletely functional activity, deliberately initiated because pleasant, non-serious, repetitive, when the subject is relaxed". Such a definition implies consciousness, especially because pleasure implies consciousness. Play can be easily recognized in mammals, birds, and lepidosaurians but has never been observed in amphibians [50], thus seems "to have been originated in amniotes" [4]. However, many fishes, especially Teleost displayed behaviors that fulfilled the criteria for play, including mental properties as established by Burghardt [50]. Bshary et al. [15] examined Fish behavior and found social strategies, social learning and tradition, and co-operative hunting that resembled those of primates including foraging skills, tool use, cognitive maps, memory, anti-predator behavior, and the manipulation of the environment.

The detour behavior, consists in being able to reach a goal with moving around an obstacle and temporary loss of the target in the process. Such a behavior, that implies a memory of the target objet, can easily be observed in mammals, birds, and reptiles but not in other animals [4]. Yet, as reminded by Rial et al. [4] such a response can be produced but pure artificial machines such as GPS; detour as a sign of consciousness should, therefore, be accepted with caution.

4. Discussion and conclusion

The theoretical and anatomical arguments, and the direct experimental evidence of sensory pleasure and signs of emotion mentioned above are an updated version of a previous paper drawing similar conclusions, but based on emotion data only [51]. They suggest that consciousness, understood not as self-consciousness but simply as the presence of a mental space, emerged in the Permian Amniotes common ancestors to present-day Sauropsides and Mammalia rather than converging emergence in those various groups (Fig. 6).

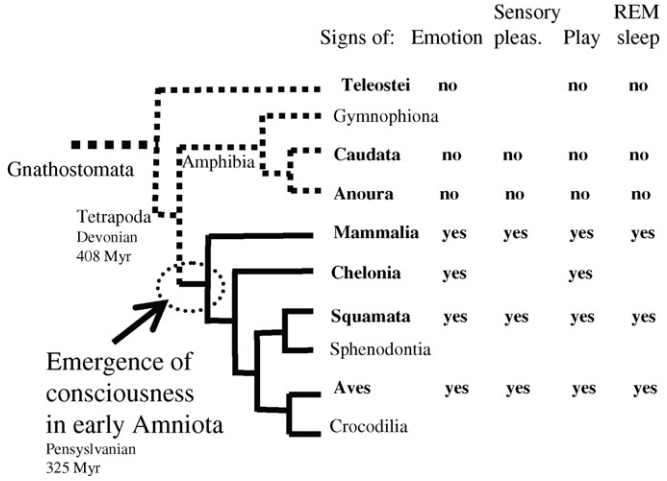

Fig. 6. Phylogenetic tree of living vertebrates (adapted from Lecointre and LeGuyader [52]). In bold the order or taxon where experimental studies provided evidence that signs of consciousness (emotion, sensory pleasure, and play behavior) and paradoxical sleep were present "yes" or absent "no".

The question of when in phylogeny did consciousness emerge, was also asked by Rial et al. [4], who studied the structure of sleep, and by Aarhem et al. [52]. Both teams also raised the possibility that consciousness might have been a quantitative (progressive) process rather than qualitative (threshold). Their conclusions on the first question was that "consciousness should have appeared in amniotes", i.e., the same as ours. In the data presented above, the presence of consciousness is suggested not from behavioral decisions or even "intelligence," – like computers that can behave and possess artificial intelligence but may not be considered as having consciousness (see McFarland [18]) – but rather from signs in the animals that exist properties indicative of consciousness defined above as a four-dimensional mental state.

Are there signs of consciousness before Amniotes? Slugs displayed aversion learning [53], Lymnaeas [54,55] and terrestrial mollusks [56,57] displayed operant conditioning of escape behavior. Yet the most striking performance was that of cephalopods who were described as playing [50] and as being able to learn by looking only [58].

These observations lead to three possibilities:

- The first is that play and these other apparently signs of consciousness, actually do not necessitate consciousness. True consciousness emerged actually with Amniotes.
- Another possibility is that elements of consciousness already showed by Mollusks and Fish are the results of convergence only, as there is a clearcut absence of any sign of consciousness among Amphibians. Thus, these early elements did not evolved to the full four-dimensional consciousness displayed in Amniotes, possibly by lack of a large enough nervous system.
- The last possibility, as suggested by Rial et al. [4], is that consciousness emerged quantitatively in phylogeny as early as Mollusks, but became exploded only with Amniotes.

If that were the case, then there would remain to find an explanation to the total absence of any sign of consciousness in Amphibians early late entails implicitly that the process was more likely to have been qualitative rather than quantitative.

The existence of consciousness in an animal does not imply that behavioral responses are rational in those animals that possess a mental space. On the contrary, this mental space may simulate several possible lines of action and use the feelings they evoke to decide which response is best. For example, hibernating mammals increase their caloric stores in the autumn, but this is not a rational choice that they make to avoid starvation during the winter. Their behavior is driven not by reason but by a fear-like emotion: a negative perception of insufficient food intake at that time of year [59]. Dictionaries provide no precise term for this kind of non-rational mental modeling when the response is purely reflexive. It may be appropriate to use mentalist terminology, i.e., emotions, feelings, etc., but only for Amniota. For other Tetrapoda and below, we should describe behavior only in terms of behavior only. Fear is clearly lacking in such organisms. Their behavioral responses that can be mimicked in artificial models [60], should be described in a way that does not imply consciousness. When a clam, for instance flees away from a predator, it does not "fear". In the case of fleeing we would suggest the use of a new word from the Latin: *timor*, to describe such non-cognitive behavioral response that precedes consciousness in phylogeny.

Consciousness may have emerged because of the increasing complexity of life in a terrestrial environment [2]. In this new adaptive landscape, existence required more and more stimulus–response pathways; eventually, a point was reached where it became more efficient, in terms of speed and flexibility, to route all decision making through a single mental space. Within this space, different possible responses would be compared and judged

according to the degree of pleasure they evoked, the aim being to maximize pleasure and to minimize displeasure. The hedonic dimension of consciousness thus became a common currency in decision making to select the final behavioral path [61,62]. It proved to be so successful that it was passed on to all descendants of these early Amniota.

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References

[1] Bering JM, Bjorklund DF. The serpent's gift: evolutionary psychology and consciousness. In: Zelazo PD, Moscovitch M, Thompson E, editors. Cambridge handbook of consciousness. New York: Cambridge University Press; 2005.
[2] Merker B. The liabilities of mobility: a selection pressure for the transition to consciousness in animal evolution. Conscious Cogn 2005;14:89–114.
[3] Cabanac M. On the origin of consciousness, a postulate and its corrollary. Neurosci Biobehav Rev 1996;20:33–40.
[4] Rial RV, et al. The evolution of consciousness in animals. In: Århem P, Liljenström H, editors. Consciousness transitions—phylogenetic, ontogenetic and physiological aspects. Amsterdam: Elsevier; 2008. p. 45–76.
[5] Cabanac M. La cinquième influence, ou La dialectique du plaisir. Québec: Presses de l'Université Laval; 2003. p. 287.
[6] Descartes R. Traité des passions de l'âme. Amsterdam: Elsevier; 1650.
[7] Darwin C. The expression of the emotions in man and the animals. Chicago: University of Chicago Press; 1872. p. 372.
[8] Watson JB. Psychology from the standpoint of a behaviorist. Philadelphia: Lippincott; 1919.
[9] Griffin DR. Animal minds. Chicago: University of Chicago Press; 1992.
[10] Dawkins MS. Through our eyes only? 1st ed. Oxford: W.H. Freeman & Co.; 1993. p. 192.
[11] McFarland DJ. Animal behaviour. London: Pitman; 1985. p. 576.
[12] Burghardt GM. Conceptions of play and the evolution of animal minds. Evol Cogn 1999;5:114–22.
[13] Jerison HJ. Evolution of the brain and intelligence. New York: Academic Press; 1973.
[14] Heyes CM. Theory of mind in non human primates. Anim Behav 1994;47:909–19.
[15] Bshary R, Wickler W, Fricke H. Fish cognition: a primate's eye view. Anim Cogn 2002;5:1–13.
[16] Gould JL, Grant-Gould C. The honey bee. New York: Scientific American Library; 1995.
[17] Bullock TH. Simple systems for the study of learning mechanisms. In: F.O.S., et al., editors. Neurosciences research symposium summaries. Cambridge, Massachusetts: MIT Press; 1967. p. 203–327.
[18] McFarland D. Defining motivation and cognition in animals. Int Stud Philos Sci 1991;5:153–70.
[19] Merker B. Consciousness without a cerebral cortex: a challenge for neuroscience and medicine. Behav Brain Sci 2007;30:63–81.
[20] Parent A. Comparative neurobiology of the basal ganglia. New York: John Wiley & Sons; 1986. p. 335.
[21] Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Rev 1998;28:309–69.
[22] Wyvell CL, Berridge KC. Intra-accumbens amphetamine increases the conditioned incentive salience of sucrose reward: enhancement of reward "wanting" without enhanced "liking" or response reinforcement. J Neurosci 2000;20:8122–30.
[23] Kudryavtseva NN. An experimental approach to the study of learned aggression. Aggr Behav 2000;26:241–56.
[24] Cabanac A, Briese E. Handling elevates the colonic temperature of mice. Physiol Behav 1991;51:95–8.
[25] Briese E, Cabanac M. Emotional fever and salicylate. In: Szelényi Z, Székely M, editors. Contributions to thermal physiology. Budapest: Pergamon-Akadémiai Kiadó; 1980. p. 161–3.
[26] Briese E, Cabanac M. Stress hyperthermia: physiological arguments that it is a fever. Physiol Behav 1991;49:1153–7.
[27] Cabanac M, Aizawa S. Fever and tachycardia in a bird (*Gallus domesticus*) after simple handling. Physiol Behav 2000;69:541–5.
[28] Cabanac AJ, Guillemette M. Temperature and heart rate as stress indicators of handled common eider. Physiol Behav 2001;74:475–9.
[29] Cabanac M, Gosselin F. Emotional fever in the lizard *Callopistes maculatus*. Anim Behav 1993;46:200–2.
[30] Cabanac M, Bernieri C. Behavioral rise in body temperature and tachycardia by handling of a turtle (*Clemys insculpta*). Behav Proc 2000;49:61–8.
[31] Cabanac A, Cabanac M. Heart rate response to gentle handling of frog and lizard. Behav Proc 2000;52:89–95.
[32] Cabanac AJ, Cabanac M. No emotional fever in toads. J Therm Biol 2004;29:669–73.
[33] Cabanac M, Laberge F. Fever in goldfish is induced by pyrogens but not by handling. Physiol Behav 1998;63:377–9.
[34] Norgren R, Grill HJ. Brain–stem control of ingestive behavior. In: Pfaff DW, editor. The physiological mechanisms of motivation. New York: Springer-Verlag; 1982. p. 99–131.
[35] Berridge KC, et al. Sodium depletion enhances salt palatability in rats. Behav Neurosci 1984;98:652–61.
[36] Cabanac M, Lafrance L. Postingestive alliesthesia: the rat tells the same story. Physiol Behav 1990;47:539–43.
[37] Breslin PAS, Davidson TL, Grill HJ. Conditioned reversal of reactions to normally avoided tates. Physiol Behav 1990;47:533–8.
[38] Berridge KC. Measuring hedonic impact in animals and infants microstructure of affective taste reactivity patterns. Neurosci Biobehav Rev 2000;24:173–98.
[39] Myers KP, Sclafani A. Conditioned enhancement of flavor evaluation reinforced by intragastric glucose. II. Taste reactivity analysis. Physiol Behav 2001;74:495–505.
[40] Cabanac M, Serres P. Peripheral heat as a reward for heart rate response in the curarized rat. J Comp Physiol Psychol 1976;90:435–41.
[41] Cabanac M. Do birds experience sensory pleasure? Evol Psychol 2009, in press.
[42] Garcia J, et al. A general theory of aversion learning. Ann N Y Acad Sci 1985;443:8–21.
[43] Paradis S, Cabanac M. Flavor aversion learning induced by lithium chloride in reptiles but not in amphibians. Behav Proc 2004;67:11–8.
[44] Cabanac M. Pleasure: the common currency. J Theor Biol 1992;155:173–200.
[45] Cabanac M. Strategies adopted by juvenile lizards foraging in a cold environment. Physiol Zool 1985;58:262–71.
[46] Balaskó M, Cabanac M. Behavior of juvenile lizards (*Iguana iguana*) in a conflict between temperature regulation and palatable food. Brain Behav Evol 1998;52:257–62.
[47] Cabanac M, Johnson KG. Analysis of a conflict between palatability and cold exposure in rats. Physiol Behav 1983;31:249–53.
[48] Cabanac M. Palatability vs. money: experimental study of a conflict of motivations. Appetite 1995;25:43–9.
[49] Nicolau MC, et al. Why we sleep: the evolutionary pathway to the mammalian sleep. Prog Neurobiol 2000;62:379–406.
[50] Burghardt GM. The genesis of animal play. Cambridge–Massachusetts: The MIT Press; 2005. p. 5001.
[51] Cabanac M. Emotion and phylogeny. Jpn J Physiol 1999;49:1–10.
[52] Lecointre G, LeGuyader H. Classification phylogénétique du vivant. 2nd ed. Paris: Belin; 2001.
[53] Aarhem P, Lindahl BIB, Manger PR. On the origin of consciousness—some amniote scenarios. In: Århem P, Liljenström H, editors. Consciousness transitions—phylogenetic, ontogenetic and physiological aspects. Amsterdam: Elsevier; 2008. p. 77–95.
[54] Delaney K, Gelperin A. Post-ingestive food-aversion learning to amino acid deficient diets by the terrestrial slug *Limax maximus*. J Comp Physiol 1986;159A:281–95.
[55] Kobayashi S, et al. Operant conditioning of escape behavior in the pond snail *Lymnaea stagnalis*. Zool Sci 1998;15:683–90.
[56] Sangha S, et al. The effects of continuous versus partial reinforcement schedules on associative learning, memory and extinction in *Lymnaea stagnalis*. J Exp Biol 2002;205:1171–8.
[57] Gelperin A. Rapid food-aversion learning by a terrestrial mollusk. Science 1975;189:567–70.
[58] Kojima S, et al. Optical detection of neuromodulatory effects of conditioned taste aversion in the pond snail *Lymnaea stagnalis*. J Neurobiol 2001;49:118–28.
[59] Denton D. The pinnacle of life. San Francisco: Harper Collins; 1994.
[60] Blumstein DT. Developing an evolutionary ecology of fear: how life history and natural history traits affect disturbance tolerance in birds. Ethology 2006;71:389–99.
[61] Blumstein DT, Bitton A, DaVeiga J. How does the presence of predators influence the persistence of antipredator behavior? J Theor Biol 2006;239:460–8.
[62] McFarland DJ, Sibly RM. The behavioural final common path. Philos Trans R Soc 1975;270:265–93.

La révolution des neurones artificiels

Traduction automatique, conduite autonome : les progrès de l'intelligence artificielle s'appuient sur les réseaux de neurones, une vieille idée relancée par les géants de l'informatique.

LE MONDE SCIENCE ET TECHNO | 09.01.2017 à 17h59 • Mis à jour le 10.01.2017 à 06h42 | Par David Larousserie

L'année 2016 aura été celle des grandes percées en intelligence artificielle. En mars, le programme AlphaGo de la filiale de Google DeepMind battait un champion coréen au jeu de go par quatre victoires à une. En juin, l'équipe chinoise du moteur de recherche Baidu annonçait des performances inégalées en traduction automatique : six points de mieux que l'état de l'art. En septembre, Google répliquait avec un point de mieux et l'intégration de cette technique dans son célèbre outil de traduction.

En novembre, une équipe d'Oxford et de Google décrivait son programme de lecture sur les lèvres, surpassant nettement les meilleurs programmes, déjà supérieurs à l'être humain. Et en décembre, à Barcelone, Nips, une conférence phare d'intelligence artificielle, accueillait 6 000 personnes, le double de l'an passé. L'année 2016 a aussi été celle des assistants vocaux à la maison (Echo d'Amazon, Home de Google…), des « robots » de conversation, des véhicules autonomes, avec son lot de désillusions : propos racistes et accident mortel, entre autres.

Le point commun de cette vague de succès est une petite révolution technique qui prend ses racines à la fin des années 1940, s'éteint presque, puis renaît et écrase la concurrence à partir de 2012, jusqu'à se répandre partout : automobile, aide au diagnostic médical, reconnaissance d'images, compréhension du langage naturel, traduction…

« Pendant longtemps, on nous a jeté des tomates », se souvient Christophe Garcia, aujourd'hui directeur du Laboratoire d'informatique en image et systèmes d'information à Lyon, mais qui a œuvré au sein des laboratoires Orange, à Rennes, pour développer cette technologie redoutablement efficace : les réseaux de neurones artificiels. *« Maintenant, je croule sous les sollicitations et, du jour au lendemain, j'ai vu des détracteurs retourner leur veste et clamer qu'ils faisaient comme moi ! »*, ajoute, amusé, le chercheur.

Lire aussi : Des intelligences artificielles lisent désormais sur les lèvres

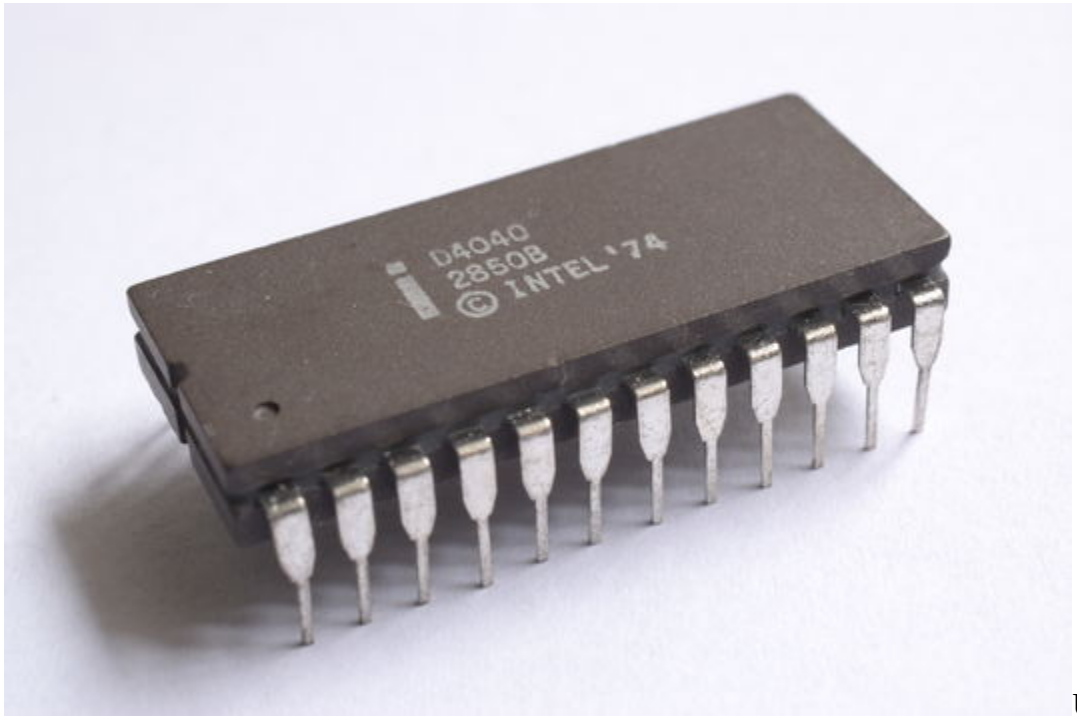
« Nos étudiants refusaient même nos sujets, car ils savaient qu'ils auraient peu de chances d'être publiés », complète Yoshua Bengio, franco-canadien, professeur à l'université de Montréal, à la tête de ce qu'il considère comme *« le plus gros groupe de recherche sur le sujet dans le monde académique »*.

Une très vieille idée

Yoshua Bengio est surtout, avec le Français Yann LeCun (aujourd'hui chez Facebook et à l'université de New York) et l'Ecossais Geoffrey Hinton (lui partage son temps entre l'université de Toronto et Google), l'un des trois chercheurs – autobaptisés « conspirateurs » – qui ont tenu bon pour promouvoir ces réseaux de neurones. Ils les ont même renommés deep learning, ou apprentissage profond, pour éviter la référence au cerveau, trop connotée négativement.

Il est vrai que cette révolution des années 2000 est une très vieille idée. Elle prend racine aux débuts de l'informatique, quand Warren McCulloch, Walter Pitts et Donald Hebb réalisent, dans les années 1940, que le cerveau étant une belle machine, il serait tentant de l'imiter. Les chercheurs retiennent de cette complexité quelques notions simples. Le cerveau est constitué de neurones reliés entre eux par des synapses. Celles-ci sont plus ou moins fortes en fonction de stimulus reçus (leur répétition, leur intensité, leur « passé »…). Les neurones réagissent en faisant la somme pondérée des informations reçues des synapses.

image: http://s1.lemde.fr/image/2017/01/09/534x0/5059946_6_6062_un-processeur-intel-d4040_5f7a8915f9c1953c8075d4eeddf2c9d0.jpg



Un processeur Intel D4040. Thomas Nguyen et Deep Dream Generator

Cela débouche même sur une machine, le perceptron de Frank Rosenblatt à la fin des années 1950, capable de reconnaître des images après une phase dite « d'apprentissage ». Les valeurs des « synapses » sont ajustées jusqu'à ce que la réponse soit correcte. Le système est ensuite capable, face à une image inconnue, de la classer dans l'une des catégories apprises (chien, chat, voiture…). Imaginez que vous vouliez obtenir une certaine couleur à partir de trois pots de peinture, rouge, jaune, bleu. Vous mettez plus ou moins de l'une et de l'autre jusqu'à trouver le bon mélange. C'est exactement ce que fait le perceptron ; les « synapses » correspondant au volume des trois couleurs.

Finalement, les descendants actuels du perceptron font toujours la même chose. Prendre des informations en entrée, modifier les « connexions » à l'intérieur pour trouver la bonne réponse, de façon à sortir de nouvelles données permettant de classer, de reconnaître et simplifier les entrées inconnues… Ce type d'intelligence se distingue de celui qui consistait à élaborer des règles à suivre pour la machine (règles de grammaire, recherche de certains traits dans une image…).

Le scepticisme des symbolistes

Mais, pendant de nombreuses années, cette belle idée n'a guère progressé. Pire, un pape de l'intelligence artificielle, Marvin Minsky, avait même démontré, dans les années 1960, que certaines tâches seraient impossibles à réaliser de cette façon. De plus, les chercheurs ne savaient pas trop comment ajuster ce -câblage complexe. Ajoutons aussi que d'autres méthodes d'apprentissage ont fleuri. La plus simple, qui fonctionne encore, est par exemple la régression linéaire. Etant donné quelques points sur une feuille, elle consiste à trouver la pente d'une droite passant le plus près possible de tous ces points, pour ensuite déterminer la réponse à une valeur inconnue.

Ultime coup de grâce, parallèlement à la vision bio-inspirée dite « connexionniste » des réseaux de neurones, s'est développée la vision « symboliste » issue notamment des travaux de von Neumann. Celle-ci sépare les unités de calcul des unités de stockage ; les résultats des unes alimentant les autres et réciproquement. Tous les ordinateurs fonctionnent désormais ainsi, contrairement à notre cerveau qui a une mémoire et des calculs distribués.

Mais les connexionnistes prennent leur revanche. A partir des années 1980, de rares travaux marquent une renaissance. Si rares et si dispersés que la généalogie est difficile à retracer pour identifier ce regain. Lorsque le trio de conspirateurs s'y essaie dans *Nature*, en mai 2015, un quatrième chercheur (comme eux au sommet des citations), Jürgen Schmidhuber, professeur à l'université de Lugano (Suisse), les tacle, corrigeant leur bibliographie.

Toujours est-il que, petit à petit, les chercheurs ont réussi à dépasser les limites du perceptron. Au milieu des années 1990, par exemple, Yann LeCun et Yoshua Bengio, au sein des laboratoires de la société américaine de télécommunications ATT, mettent au point une machine de reconnaissance de caractères manuscrits. Autre progrès en 2008, la reconnaissance automatique des visages et des plaques d'immatriculation par Google, afin de les flouter dans Google Street View.

Lire aussi : Des composants bio-inspirés

Surtout, l'équipe de Geoffrey Hinton démontre magistralement, en 2012, que les nouveaux réseaux de neurones fonctionnent mieux que les anciens, et même que toutes les techniques concurrentes pour la reconnaissance d'images. Lors de la compétition de classification d'images Imagenet, leur programme ne fait que 15 % d'erreurs quand le second au classement en faisait 25 %. En 2013, toutes les équipes ou presque utilisaient l'apprentissage profond…

Renaissance

Cette renaissance est due à trois facteurs. D'abord, pour apprendre à ce cerveau de silicium à bien régler ces synapses, il doit se nourrir d'exemples. Il faut des millions d'images, nécessairement annotées, les décrivant afin de dire à la machine si elle a tort ou raison. A partir des années 2000 et la montée en puissance de la numérisation, de telles collections se créent pour les lettres manuscrites, les images, les langues…

Ensuite, même si les opérations sont très simples (des additions et des multiplications essentiellement), il faut en mener énormément, ce qui est gourmand en calculs. Les ingénieurs ont bénéficié là des progrès des fabricants qui, pour les jeux vidéo, ont développé des processeurs particuliers, dits « graphiques » (GPU en anglais), parfaits pour répéter souvent le même genre d'opération simple.

Enfin, les chercheurs se sont creusé la tête pour améliorer astucieusement ces algorithmes : architecture en plusieurs couches de neurones, procédure pour corriger le câblage interne en fonction de la sortie, « filtres » mathématiques pour traiter adroitement les signaux d'entrée… Geoffrey Hinton a aussi montré qu'un apprentissage un peu simple rend trop rigide le réseau et conduit à des erreurs. Il introduit donc un peu d'aléa afin de perturber les synapses et de rendre plus plastique sa machine.

« Il y a quinze ans, on aurait pensé que c'était inaccessible, voire de la science-fiction »
Yann Ollivier, chercheur CNRS à l'université Paris-Saclay

« Il y a quinze ans, on aurait pensé que c'était inaccessible, voire de la science-fiction. Mais cette progression a fini par déboucher ! », estime Yann Ollivier, chercheur CNRS à l'université Paris-Saclay. Depuis, c'est donc le succès, avec une foule de variations et d'améliorations permettant des prouesses spectaculaires. Les réseaux peuvent avoir des dizaines de couches, un million de neurones et des milliards de synapses. Ils sont capables d'identifier un sport dans une vidéo. Ils peuvent prédire la suite d'une phrase ou même d'une vidéo. Ils peuvent additionner deux visages de manière à poser les lunettes de l'un sur le visage de l'autre.

« Boîte noire »

De nombreuses variantes ont essaimé. DeepMind s'est spécialisé dans la technique de l'apprentissage par renforcement : la machine s'est améliorée au go en jouant contre elle-même – récemment, sa dernière version a anonymement écrasé en ligne les meilleurs joueurs humains. Yann LeCun et son équipe de

Facebook ont développé l'apprentissage adversariel : deux réseaux de neurones se confrontent ; l'un essayant de tromper l'autre. C'est ainsi qu'ils prédisent les séquences d'un film.

Jürgen Schmidhuber les a dotés d'une sorte de mémoire à court terme en interconnectant les couches. L'entreprise française Spikenet a trouvé un moyen de reconnaître en une fois certains objets, en se basant sur l'ordre d'apparition des signaux dans les synapses plutôt que leur intensité. Ses caméras repèrent, dans les casinos, les cartes ou les dés, pour détecter les fraudes.

Les géants de l'informatique, Google, Facebook, Microsoft, IBM, Baidu… recrutent à tour de bras et mettent à disposition des logiciels (Torch, Tensorflow, PaddlePaddle, Caffe…) pour faciliter l'écriture de programmes. Nvidia, fabricant de cartes graphiques, a lancé un premier ordinateur dédié…

« Ça marche très bien, mais n'en comprend pas très bien le fonctionnement »
Emmanuel Mogenet, directeur du laboratoire de recherche de Google à Zürich

Lire aussi : Contrôler des neurones par ultrasons

Où cela va-t-il s'arrêter ? *« Ça marche très bien, mais c'est un peu une boîte noire. On n'en comprend pas très bien le fonctionnement*, indique Emmanuel Mogenet, directeur du nouveau laboratoire de recherche de Google à Zürich, ouvert il y a un an et déjà fort de plus de 130 chercheurs. *Comme l'alchimie au Moyen Age, ça reste assez empirique. »*

A chaque « problème », l'ingénieur hésite : combien de couches de neurones faudra-t-il ? De paramètres ? Quelles fonctions mathématiques choisir pour estimer les erreurs d'apprentissages et les corriger ? Comment ne pas avoir un système trop « rigide » ? Trop complexe ?

« Action/réaction »

Pire, un autre article, cité plusieurs fois, d'une équipe issue de Google, Facebook et de l'université de Montréal en 2013 a montré qu'un réseau de neurones de reconnaissance d'images prenait un chien ou une mante religieuse pour une autruche, alors que seuls quelques pixels de l'image, invisibles à l'œil, avaient été modifiés…

« Nous avons encore du chemin à parcourir avant d'avoir des réseaux de neurones capables de raisonner ou de faire des choses compliquées à partir de peu d'informations », estime Geoffrey Hinton. AlphaGo ne sait pas par exemple qu'il joue au go. Ces réseaux sont de plus surtout efficaces pour des problèmes de type assez fruste « action/réaction », loin de représenter toutes les tâches cognitives.

En taille, les réseaux actuels sont également très loin des 100 milliards de neurones d'un cerveau humain et de leurs nombreuses relations. Chacun est entraîné et réservé à une fonction particulière : pas simple de mettre ensemble une machine de go et un traducteur… Leur succès a aussi réveillé les interrogations éthico-sociales sur leurs applications : nouveau type d'armes autonomes, emplois remplacés par des automates, responsabilité en cas de faute, contrôle des boîtes noires, gestion des données personnelles nourrissant les algorithmes…

Marge de progression

A court terme, Yoshua Bengio, l'une des rares vedettes non débauchées par l'industrie (mais qui a des contrats avec elle), souligne *« le risque qu'on manque de profs pour former les jeunes ». « Il ne faudrait pas commettre la même erreur que lors des prémices des réseaux de neurones et se fermer à d'autres idées »*, indique pour sa part Christophe Garcia, qui note aussi que, parfois, une *« régression linéaire classique peut suffire à régler un problème »*.

Les défis à relever sont aussi encore nombreux. De grandes masses de données sont nécessaires pour entraîner ces réseaux pour la phase d'apprentissage dit « supervisé », et celles-ci n'existent pas toujours. Certains essaient de pallier ce défaut en utilisant des réseaux éprouvés sur une tâche pour leur en faire faire une autre.

L'un des Graal est de parvenir à un apprentissage non supervisé, c'est-à-dire que le réseau apprendrait tout seul en observant, sans nécessité de lui faire ingurgiter des collections annotées de données. Pour Yann - LeCun, lors de la séance inaugurale de ses cours au Collège de France, en 2016, *« dans la métaphore de la cerise sur le gâteau, le supervisé, c'est la cerise et le non-supervisé, c'est le gâteau »*. Il y a donc de la marge de progression.

En savoir plus sur http://www.lemonde.fr/sciences/article/2017/01/09/la-revolution-des-neurones-artificiels_5059943_1650684.html#VdvWV1T7tXIlHPQS.99

Ventral striatal plasticity and spatial memory

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Spatial memory formation is a dynamic process requiring a series of cellular and molecular steps, such as gene expression and protein translation, leading to morphological changes that have been envisaged as the structural bases for the engram. Despite the role suggested for medial temporal lobe plasticity in spatial memory, recent behavioral observations implicate specific components of the striatal complex in spatial information processing. However, the potential occurrence of neural plasticity within this structure after spatial learning has never been investigated. In this study we demonstrate that blockade of cAMP response element binding protein–induced transcription or inhibition of protein synthesis or extracellular proteolytic activity in the ventral striatum impairs long-term spatial memory. These findings demonstrate that, in the ventral striatum, similarly to what happens in the hippocampus, several key molecular events crucial for the expression of neural plasticity are required in the early stages of spatial memory formation.

cAMP response element binding protein | nucleus accumbens | tissue plasminogen activator | Morris water maze | mice

The formation of long-term memories is believed to involve a dynamic process by which a labile memory is progressively converted into a more stable and potentially permanent trace. Evidence for such a time-dependent process comes from studies demonstrating that electroconvulsive shock produces amnesia only if delivered shortly after learning, whereas the same treatment is ineffective when delivered several hours later (1). Long-term memory is accompanied by changes in neuronal morphology and connectivity, and these alterations are thought to be essential for the stabile encoding of new information (2). This transformation has been suggested to depend upon plastic changes that involve a sequence of specific and coordinated cellular processes. These begin with neurotransmitter receptor activation that induces short-term changes in synaptic efficacy based on receptor phosphorylation and trafficking (3, 4). Subsequently, alterations in gene expression and protein synthesis occur that are the basis for long-term structural modifications (5, 6).

A key issue in the study of memory in vertebrates is the brain site at which these processes occur. Clinical evidence in humans suggests that structures within the medial temporal lobe (MTL) play a prominent role in long-term memories. MTL lesions induce profound deficits in the formation of long-lasting declarative memories while sparing the acquisition of nondeclarative memories such as visual-motor skills (7, 8). Such findings suggest that the hippocampus might be an essential site where plasticity occurs in the initial steps of declarative memory stabilization. Accordingly, those molecular events thought to be crucial for the long-term encoding of memories such as regulation of gene expression and protein synthesis, as well as structural changes, have been described in the hippocampus after spatial learning (6, 9, 10).

Recent experimental evidence, however, demonstrates that structures different from the hippocampus might also be involved in the acquisition of spatial information. In this regard it is interesting to note that altered activity of the striatal complex can impair the ability to perform spatial learning tasks (11, 12). These findings could be the result of a requirement for neurotransmission in the ventral striatum (VS) in facilitating the proper flow of information or, alternatively, in the induction of plasticity needed for long-term stabilization of critical information necessary for spatial navigation.

Thus, to investigate the possible role of the VS in the stabilization of spatial memories, we tested whether different key molecular events shown to be crucial for hippocampal-dependent memory formation, such as cAMP response element binding protein (CREB) activity, de novo protein synthesis, and ECM remodeling, were needed within the VS to ensure the stabilization of new spatial memories.

Results

CREB Activity in VS Is Required for Spatial Memory Consolidation. Fig. 1*A* shows the effect of pretraining administration of antisense or sense CREB oligonucleotides or vehicle into the VS on spatial memory measured 24 h after training in the spatial discrimination task. Values are expressed as an index of reexploration, representing the difference between exploration of the displaced objects in session 5 (S5) and exploration of the same object category in session 4 (S4). Mice injected with vehicle or sense CREB oligonucleotide showed equivalent performance, reexploring the displaced object significantly more than the nondisplaced object. Mice receiving antisense CREB oligonucleotide showed a significantly lower level of relative exploration of the displaced object compared with the other groups [ANOVA of treatment, $F(1,22) = 3.475$; $P = 0.0757$; treatment × object category, $F(1,22) = 21.875$; $P = 0.0001$]. To examine whether antisense CREB oligonucleotide was able to suppress both short- and long-term memory recall, a similarly treated group of mice underwent testing 3 min after training. In contrast to the group tested 24 h after training, this group showed no significant effect of treatment on spatial memory recall as measured by relative exploration of the displaced object [Fig. 1*B*; ANOVA of treatment, $F(1,17) = 0.084$; $P = 0.7749$; object category, $F(1,17) = 28.138$; $P = 0.0001$; treatment × object category, $F(1,17) = 0.170$; $P = 0.6857$). To extend this finding we assessed the effects of CREB injections into the VS on spatial memory performance in the Morris water maze task. The mice were trained in a water maze using a single-day massed procedure (12). As previously observed in the spatial discrimination task vehicle and sense CREB oligonucleotide injected mice 24 h after training showed similar performance spending more time in the correct quadrant

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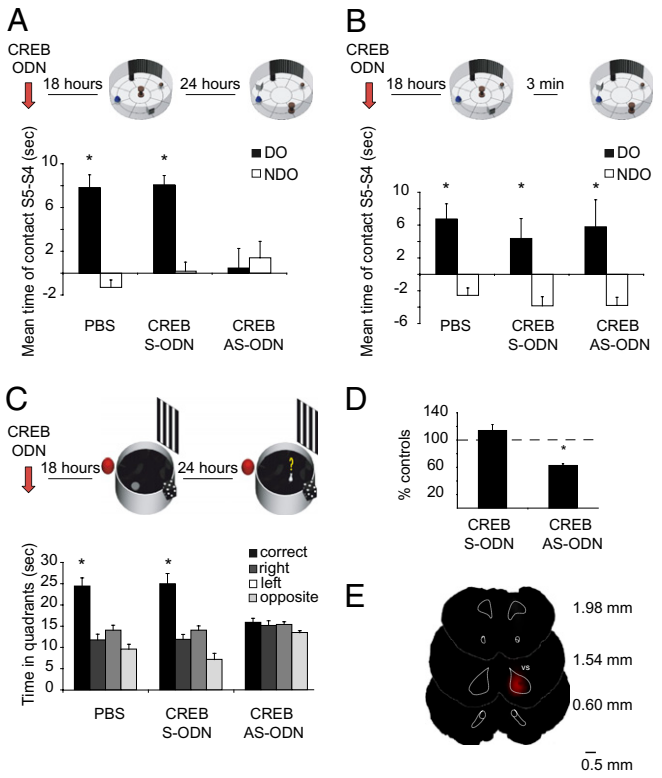

Fig. 1. Antisense oligonucleotide (CREB-AS) complementary to the CREB coding sequence injected into the VS 18 h before training impairs long-term (*A*) but not short-term (*B*) memory for object position. Focal administrations of PBS solution or of the sense oligonucleotide (CREB-S) were always ineffective. The histogram illustrates the mean time (±SEM) spent exploring the displaced objects (DO) and the nondisplaced objects (NDO) in S5, minus the time spent exploring the same class of objects in the last session of habituation (S4). $*P < 0.05$, DO vs. NDO within groups. Administrations of CREB-AS but not CREB-S or PBS solution impaired mice's ability to locate the platform during the probe test in the water maze if the animals were tested 24 h later (*C*). The histograms represent the mean time (in sec ± SEM) spent in the four quadrants. $*P \leq 0.05$, correct vs. opposite, right, left quadrants, within groups. §$P \leq 0.05$, correct quadrant, CREB-S vs. CREB-AS group. (*D*) CREB protein immunoreactivity in the VS is decreased in mice focally injected with CREB AS-ODN compared with CREB-S-ODN–injected mice. Each bar represents the percentage change in respect to PBS solution controls of two different experiments. $*P < 0.05$, CREB-S vs. CREB-AS. (*E*) Representative photomicrographs of coronal section through the VS showing the pattern of diffusion of fluorescent CREB-AS-ODN after the injection.

than in the other three. To the contrary, mice injected with antisense CREB oligonucleotide spent equivalent time in the four quadrants during the probe trial, thus proving to be unable to correctly locate the platform [Fig. 1*C*; ANOVA of treatment, $F(1,15) = 4.208$; $P = 0.056$; quadrant preference, $F(3,45) = 17.131$, $P = 0.0001$; treatment × quadrant preference, $F(3,45) = 10.774$; $P = 0.0001$]. To confirm that suppression of CREB expression was restricted to mice treated with antisense CREB oligonucleotide, we examined levels of CREB protein in tissue punches of VS from mice, administered 18 h earlier with vehicle or sense or antisense CREB oligonucleotide. Antisense CREB oligonucleotide treatment was associated with a 40% decrease in CREB immunoreactivity compared with sense-treated control mice [Fig. 1*D*; $F(1,2) = 31.47$; $P = 0.03$]. No difference in CREB immunoreactivity was detected between sense oligonucleotide and vehicle-treated control mice. To determine whether the effects induced by antisense CREB oligonucleotide could be attributed to its action within the VS or to its spreading outside this brain region, we injected Cy-3–labeled antisense CREB oligonucleotide into the VS. Fluorescent oligonucleotide, labeled a sphere with a radius of approximately 0.5 mm from the point of injection (0.52 ± 0.06 mm ventral, 0.58 ± 0.03 mm lateral, and 0.56 ± 0.04 mm anterior to the injection site). Therefore, in most cases, the extension of the oligodeoxynucleotide (ODN) distribution did not exceed the border of the VS (Fig. 1*E*).

Overall, these data suggest that a certain minimum level of CREB protein is required in the VS for long-term, but not short-term, recall of spatial memory.

Protein Synthesis in VS Is Required for Spatial Memory Consolidation. To block protein synthesis during the immediate posttraining consolidation period and to rule out an effect of the drug on training itself, we administered anisomycin into the VS immediately after training and tested the animals 24 h later in the spatial discrimination task. Fig. 2*A* shows the effects of anisomycin administrations on long-term spatial memory recall as measured by relative exploration of the displaced object during S5. Mice receiving the high doses of anisomycin showed significantly lower memory than mice treated with the low dose or vehicle [Fig. 2*A*; ANOVA of treatment, $F(3,32) = 0.725$; $P = 0.5446$; object category, $F(1,32) = 11.86$; $P = 0.0016$; treatment × object category, $F(3,32) = 7.552$; $P = 0.0006$]. Next we assessed the effects of immediate posttraining injections of anisomycin into the VS on spatial memory performance in the Morris water maze task. Immediately after the final training session, mice were administered 100 μg anisomycin per side and tested in a probe trial 24 h later (Fig. 2*B*). As shown in Fig. 2*B*, control mice spent more time in the correct quadrant compared with other three quadrants, thus showing a correct memory for the platform location. To the contrary, mice administered anisomycin spent similar amount of time

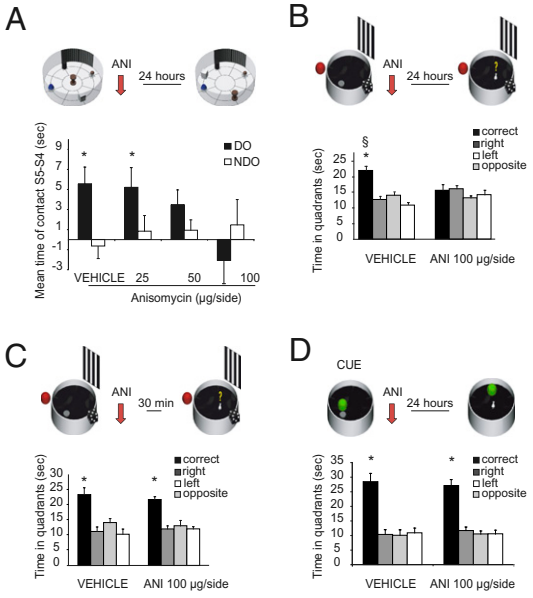

Fig. 2. (*A*) Reactivity to spatial change was impaired 24 h after the immediate posttraining ventral striatal administration of anisomycin 50 and 100 μg per side, but not after vehicle or anisomycin 25 (μg per side). The histogram illustrates the mean time (±SEM) spent exploring the DO or NDO in S5, minus the time spent exploring the same class of objects in the last session of habituation (S4). $*P < 0.05$, DO vs. NDO within groups. Immediate posttraining administrations of anisomycin (100 μg per side) impaired mice's ability to locate the platform during the probe test in the water maze if the animal were tested 24 h (*B*) but not 30 min (*C*) after training or in the cue version of the water maze 24 h after training (*D*). The histograms represent the mean time (±SEM) spent in the four quadrants. $*P \leq 0.05$, correct vs. opposite, right, left quadrants, within groups. §$P \leq 0.05$, correct quadrant, PBS vs. anisomycin group.

in the four quadrants [Fig. 2*B*; ANOVA of treatment, $F(1,14) = 1.95$; $P = 0.18$; quadrant preference, $F(3,42) = 7.95$; $P = 0.0003$; treatment × quadrant preference, $F(3,42) = 5.64$; $P = 0.0024$). To verify whether the effects observed were specific for long-term memory, in a separate experiment, anisomycin-treated mice were tested 30 min after training. In this case, no difference was found between control and anisomycin-treated mice [Fig. 2*C*; ANOVA of treatment, $F(1,14) = 0.119$; $P = 0.73$; quadrant preference, $F(3,42) = 20.41$; $P = 0.0001$; treatment × quadrant preference, $F(3,42) = 0.45$; $P = 0.715$]. A caveat to be considered when using posttraining administrations is the possibility that the effects observed could be caused by nonmnemonic proactive effects of the drug on probe trial performance. The similar response observed in mice administered immediately after training and tested with a ST interval, however, seems to exclude this possibility.

Finally, we asked whether the effect observed was specific to spatial learning or could be a result of impairments in nonspatial components of the task. To this end we tested the effects of immediate posttraining administration of 100 μg anisomycin per side in the VS in the cue version of the water maze, in which mice were required to approach the platform by associating it with a single visual cue. Anisomycin-treated mice performed similarly to control animals spending more time in the correct quadrant than in the other three [Fig. 2*D*; ANOVA of treatment, $F(1,15) = 0.828$; $P = 0.3772$; quadrant preference, $F(3,45) = 57.11$; $P = 0.0001$; treatment × quadrant preference, $F(3,45) = 0.726$; $P = 0.541$]. These findings suggest that inhibition of protein synthesis in the VS during the period closely following training specifically blocks the formation of long- but not short-term spatial memory. We would like to mention that the similar effects observed in two spatial learning tasks that are different in terms of motivational and motor demand and in which no overtraining is required, as well as the lack of effect in the cue version of the Morris water maze, makes it highly unlikely that the effects observed could be a result of impairments in nonspatial components of the task such as rewards or motor learning. Furthermore, the posttraining manipulation we chose to perform should be particularly suitable for ruling out possible effects of the drugs on behavioral or attentional processes.

Tissue Plasminogen Activator Activity in VS Is Required for Spatial Memory Consolidation. It has been shown that degradation of the ECM in the hippocampus by proteases such as tissue plasminogen activator (tPA)/plasmin system facilitates long-term plasticity (13) a mechanism that is thought to occur because of the relieve of the inhibitory role of ECM on synaptic remodeling (14, 15). To determine whether tPA activity in the VS was required for spatial memory consolidation, we examined long-term object place association memory in mice treated in the VS, immediately after training, with the tPA inhibitor PAI-1. Administration of PAI-1 to the VS significantly and dose-dependently decreased spatial memory recall 24 h after training compared with vehicle-treated mice as measured by relative exploration of the displaced object [Fig. 3*A*; ANOVA of treatment, $F(4,38) = 1.580$; $P = 0.19$; object category, $F(1,38) = 56.65$; $P = 0.0001$; treatment × object category, $F(4,38) = 7.228$; $P = 0.0002$]. To extend this finding, in a further experiment, we assessed the effects of immediate posttraining injections of PAI-1 into the VS on spatial memory performance in the Morris water maze task. Mice were trained in the water maze, administered immediately after the final training session with 0.5 μg PAI-1 per sode, and tested in a probe trial 24 h later. Fig. 3*B* shows the time spent in the four quadrants of the water maze during the probe trial. Control mice spent significantly more time in the correct quadrant compared with the other three quadrants, thus demonstrating correct memory for the platform location. PAI-1–treated mice, however, failed to show a preference for any quadrant during the probe trial [Fig. 3*B*; ANOVA of treatment, $F(1,15) = 1.430$; $P = 0.25$;

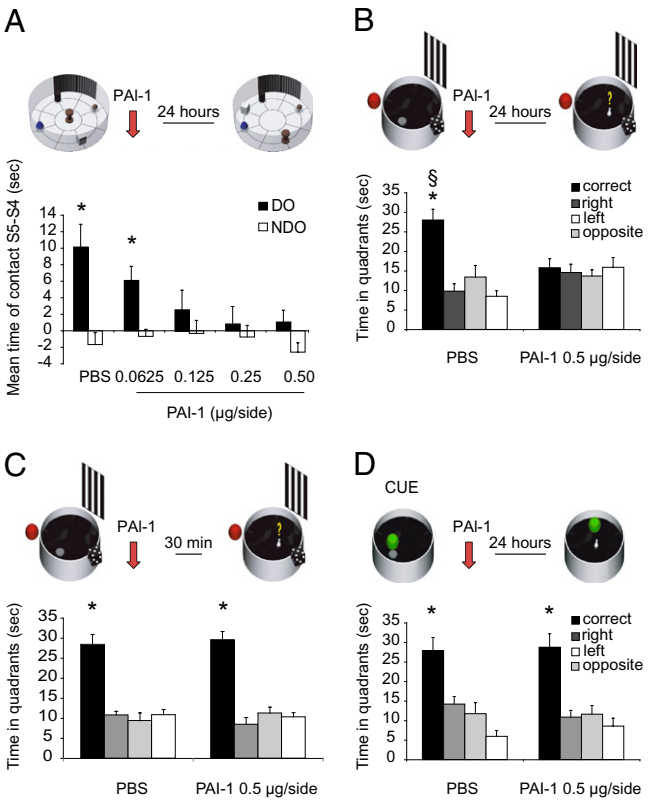

Fig. 3. (*A*) Ventral striatal administrations of PAI-1 (0.0625, 0.125, 0.25, and 0.50 μg per side) immediately after training impairs spatial discrimination 24 h after training in a dose-dependent manner. The histograms represent the mean time (±SEM) spent exploring the DO and NDO category in S5, minus the time spent exploring the same objects category in the last session of habituation (S4). *$P < 0.05$, DO vs. NDO within groups. Immediate posttraining administrations of a high dose of PAI-1 (0.5 μg per side) impaired mice's performance during the probe test in the water maze if mice were tested 24 h (*B*) but not 30 min (*C*) after spatial training, or in the cue version of the water maze 24 h after training (*D*). The histograms represent the mean time (±SEM) spent in the four quadrants. *$P \leq 0.05$, correct vs. opposite, right, left quadrants, within groups. §$P \leq 0.05$, correct quadrant, PBS vs. PAI-1 group.

quadrant preference, $F(3,45) = 6.368$; $P = 0.001$; treatment × quadrant preference, $F(3,45) = 5.506$; $P = 0.001$]. In a separate experiment, posttraining ventral striatal PAI-1 treatment was shown to have no effect on probe trial performance when animals were tested 30 min following the last training session [Fig. 3*C*; ANOVA of treatment, $F(1,14) = 0.033$; $P = 0.85$; quadrant preference, $F(3,42) = 20.875$; $P = 0.001$; treatment × quadrant preference, $F(3,42) = 0.383$; $P = 0.76$]. The specificity of the effect observed in the spatial version of the water maze after intra-VS administrations of PAI-1 was evaluated in mice trained in the cue version of the task and treated immediately posttraining with 0.5 μg PAI-1 per side. As shown in Fig. 3*D*, PAI-1 did not affect performance of the mice, with both groups spending more time in the correct quadrant than in the other three [ANOVA of treatment, $F(1,15) = 0.241$; $P = 0.631$; quadrant preference, $F(3,45) = 46.489$; $P = 0.001$; treatment × quadrant preference, $F(3,45) = 0.388$; $P = 0.7618$]. These data demonstrate that tPA activity is required immediately after spatial learning for long-term, but not short-term, memory.

tPA has a wide spectrum of putative targets that include plasminogen (16), ECM components (17), cell adhesion molecules (18), and membrane receptors (19, 20). However, it has been shown that the effects of tPA on ECM depend on its ability to cleave the

plasminogen into plasmin, whereas its effects on membrane receptors are plasminogen-independent (19, 20). To examine which of these tPA-dependent pathways might be responsible for the effects of intrastriatal PAI-1 on long-term spatial memory, we performed a quantitative assessment of plasminogen immunoreactivity in the VS of mice injected with either vehicle or PAI-1, this last group either subjected or not subjected to massed training in the Morris water maze task. Quantitative immunoblotting (Fig. 4*B*) revealed a significant decrease in plasminogen levels in trained animals compared with nontrained animals and this effect was blocked in PAI-1–treated mice [Fig. 4*A*; naive vs. trained/PBS solution, $F(1,8) = 5.295$; $P = 0.0504$; naive vs. trained/PAI-1, $F(1,8) = 0.180$; $P = 0.6829$]. These data demonstrate that spatial learning is accompanied by an increase in the proteolysis of plasminogen by tPA and suggest that plasminogen-dependent proteolytic pathway in the VS may play a role in spatial memory consolidation.

Histological Verification. A schematic representation of the injection placements for all groups of the three experiments is included in *SI Text*. Only animals showing correct VS placements were included in the statistical analysis.

Discussion

Our data show that interfering with CREB-induced transcription, protein synthesis, and reorganization of synaptic proteins in the VS impairs the ability to store spatial information. Current consolidation theory posits that a series of cellular and molecular processes within the MTL are needed during and immediately after learning to store a persistent memory trace. The formation of the trace is a dynamic process involving posttranslational protein modification and changes in gene expression (3–5, 21). These events culminate in modifications in the number and strength of synaptic connections (9) that might represent the structural trace of the memory engram [reviewed by Lamprecht and LeDoux (2)]. Interfering with any of these steps in the MTL impairs long-term memory storage. In this study we demonstrate that, for the successful consolidation of spatial information, the occurrence of such molecular processes is also required within the VS.

CREB is a ubiquitous transcription factor whose phosphorylation at serine-133 is required to trigger gene transcription underlying long-term memory consolidation. Mice lacking $CREB^{\alpha\Delta}$ (21) or carrying a mutation of serine-133 to alanine (22) show severe deficits in spatial learning tasks. Importantly, such deficits were observed only when animals were tested 24 h after training, but not a few hours after training, supporting the hypothesis that CREB-mediated transcription is selectively required for long-term maintenance of spatial information (21). In the present study we demonstrate that antisense-mediated suppression of CREB expression in the VS severely compromises spatial memory retention. Also in this case, the impairment was observed when testing was performed 24 h after training (Fig. 1 *A* and *C*) but not shortly after training (Fig. 1*B*). The lack of effect observed when there is a short delay between training and testing makes it unlikely that the deficit observed could be caused by an inability to acquire or retrieve spatial information. Furthermore, the absence of an observable effect of the control oligonucleotide on object displacement recognition (Fig. 1*A*), as well as on platform location in the spatial version of the water maze (Fig. 1*C*), argues against a possible cytotoxic effect induced by oligonucleotide infusion. Taken together, these findings suggest that normal levels of CREB expression within the VS are required to stabilize spatial information. This result resembles those reported after manipulation of the hippocampal complex. Indeed, antisense-mediated down-regulation of CREB expression within the hippocampus immediately after training has been shown to block spatial memory (10), whereas viral-mediated overexpression of CREB facilitated retention without affecting the acquisition of spatial information (23).

We next demonstrate that posttraining injection of anisomycin into the VS blocks long-term memory in the spatial discrimination task and in the Morris water maze (Fig. 2). Blockade of protein synthesis by intrahippocampal administration of the protein synthesis inhibitors has been shown to interfere with spatial memory consolidation in a diverse range of tasks, including the Morris water maze (24) and contextual fear conditioning tests (25). However, until now, a requirement for protein synthesis in spatial memory consolidation outside of the hippocampus has not been investigated. Thus, our findings support a requirement for protein synthesis outside the hippocampus to stabilize spatial information.

The long-term stabilization and storage of information in the brain has been postulated to depend upon structural changes such as altered synaptic contacts and increased or decreased number of synaptic release sites (2). Remodeling of the ECM is known to facilitate synaptic remodeling (14, 15) and several studies provide strong support for a role of extracellular proteases in facilitating synaptic plasticity and learning (26, 27). For example, focal application of tPA facilitates—whereas similar treatments with tPA inhibitors block—late-phase long-term potentiation in the hippocampus (13, 14) and tPA-KO mice show impaired persistence of hippocampal long-term potentiation (28). At the same time, tPA-KO mice show deficits in long-term spatial memory tasks (29). Interestingly, tPA-KO mice also show impaired persistence of striatal long-term potentiation and long-term depression (30), suggesting a similar role for ECM in restricting synaptic plasticity in this structure. Our finding that posttraining PAI-1 administration impairs long-term recall of memory in two different spatial learning tasks (Fig. 3 *A* and *B*) but not in a cue learning task (Fig. 3*D*) demonstrates that tPA activity in VS is specifically required for stabilization of long-term spatial memory traces. Thus, it appears that ECM-dependent structural remodeling is required in striatal circuits for successful stabilization of spatial memories.

Although the direct substrates of tPA that mediate this remodeling function are still poorly defined, our results suggest that activation of plasminogen is an essential step in this process (Fig. 4 *A* and *B*). Several studies have shown that tPA function is also essential for short-term memory (measured within 2 h of acquisition) (29). These findings suggest that, in addition to its known effects on ECM proteins, tPA may also have a more rapid function in the cleavage of critical membrane-bound targets such as NMDA receptors (20). However, we failed to observe effects of PAI-1 in the Morris water maze when the probe trial was presented 30 min after training (Fig. 3*C*). This result indicates that long-term spatial memory stabilization in VS might be mediated through the plasminogen proteolytic activity, rather than tPA-induced receptor cleavage. In fact, altered functionality of NMDA receptor in the VS would have affected also short-term memory maintenance (12).

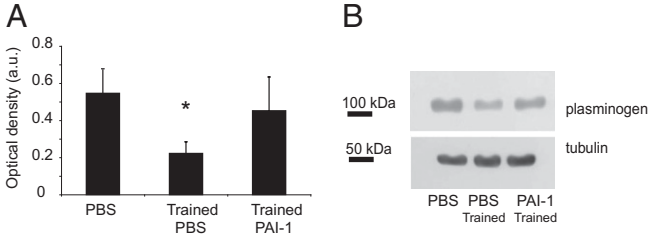

Fig. 4. Plasminogen protein levels were analyzed in the VS of mice injected with PBS solution, trained and injected with PBS solution, or trained and injected with PAI-1. (*A*) The bar graph of the densitometric analysis of the plasminogen immuno-positive bands shows a significant reduction in trained mice injected with PBS solution but not in those injected with PAI-1 (0.5 μg per side). *$P \leq 0.05$ vs. PBS solution group. (*B*) Representative immunoblot of plasminogen protein expression in the three experimental groups, with tubulin used as internal control.

Overall our data strongly suggest that plasticity within the VS is an essential requirement for long-term storage of spatial memory. Currently there are two main models of memory consolidation: the system consolidation theory and the multiple trace theory (31, 32). Independently of the model, neural plasticity within the MTL is viewed as central to store declarative information. The present finding expands this view, providing experimental evidence that the ability to encode spatial information also requires transcriptional events and synaptic remodeling within the VS, thereby suggesting that plasticity of VS and MTL is necessary. It should be mentioned that the list of brain areas involved is probably longer, entailing that long-term maintenance of spatial information is supported by neural plasticity occurring over a widespread network. This may be needed to sustain activity over a large reverberating brain circuit to permit the formation of permanent higher-level associations on the basis of the information initially stored arbitrarily following the learning experience (33). A further issue is the timing in the molecular and cellular events in the different brain structures. In analogy with current models of memory consolidation, plasticity in the VS might serve as a locus for memory storage, much as has been hypothesized for the hippocampus (32). Alternatively, plasticity in the VS may serve to sustain brain activity before the permanent transfer of spatial information to cortical structures (31). In this study we provide evidence for structural plasticity in the VS in the period that immediately follows the learning experience, but further studies will be needed to assess the stability of such changes.

The striatum and the hippocampus are generally viewed as components of distinct memory systems, the first related to habit formation and the second mediating the acquisition of spatial and episodic memories (34, 35). This model is supported by studies demonstrating dissociation in the effects induced by manipulations of the two structures in the cue or the spatial version of the Morris water maze (36) or in the cross maze task (37). The VS has been traditionally linked to motor and motivational processes (38). However, manipulations of this structure reliably produce deficits in spatial learning tasks (11, 12; but see also ref. 39). In this study we demonstrate that the molecular processes regarded as crucial for long-term stabilization of information are needed within this structure for spatial but not cue learning. This dissociation is similar to what is observed in the hippocampus (40). However, differently from the hippocampus, VS manipulations also impair responding to cues in auto-shaping, in Pavlovian-instrumental transfer, or in the early stages of instrumental conditioning, coherently with the high number of reward-responding neurons in this structure but not in the hippocampus (41).

In conclusion, our findings raise the possibility that spatial information is stored over a distributed network comprising MTL and subcortical structures. Accordingly, the storage of spatial information within MTL structures might be needed to identify changes in spatial context, whereas striatal circuits might help defining the context in which an adaptive response should occur by integrating spatial with reward related information about the salience of goal-directed behavioral adaptation.

Materials and Methods

Subjects. Male CD1 mice (Charles River) were used in the present study. Upon arrival, animals were housed in groups of five in standard breeding cages placed in a rearing room at a constant temperature (22 ± 1 °C), with food and water ad libitum. At the time of testing, they were 9 to 10 weeks old and their weights ranged from 35 to 40 g. All experiments were run during the light period (between 0900 and 1600 hours). Every possible effort was made to minimize animal suffering and all procedures were conducted according to Italian and European laws and regulations on the use of animals in research and National Institutes of Health guidelines on animal care.

Surgery. Mice underwent surgery 1 week after their arrival. They were anesthetized with an i.p. injection of chloral hydrate (500 mg/kg; Fluka) and placed in a stereotaxic frame (David Kopf Instruments). The head skin was cut longitudinally and bilateral guide cannulae (7 mm in length, 0.5 mm in diameter) were fixed on the calvarium with dental acrylic (Shofu). The following coordinates were used: anterior to bregma, +1.7 mm; lateral to midline, ±1 mm; ventral from the dura, –2.3 mm, according to the Mouse Atlas (42). Mice were left in their home cages for at least 1 week before all behavioral tests.

To verify ODN tissue diffusion, the animals underwent the surgical procedure as described earlier and the same anteroposterior and lateral coordinates were used. However, no guide cannulae were implanted. Surgery ended after the injection made by lowering a needle –4.3 mm ventral from the dura.

Drugs and Infusion. Two sequences of unmodified ODNs were used. The sequences of CREB antisense (AS-ODN) and sense (S-ODN), chosen according to previous studies (10), were as follows: CREB antisense 5′-TGGTCATCTA-GTCACCGGTG-3′; CREB sense 5′-CACCGGTGACTAGATGACCA-3′. HPSF-purified ODN (MWG Biotech) were resuspended in PBS solution (pH 7.4). Either AS-ODN or S-ODN was administered at the dose of 4.0 nmol per side.

ODN tissue diffusion was studied using AS-ODNs coupled at their 3′-end with the Cy3 fluorescent dye (Biofab). The labeled and unlabeled ODNs were mixed in a 50% ratio and resuspended in PBS solution. The concentration and the volume of injected solutions were the same as in the behavioral experiment (4.0 nmol per side).

Doses of anisomycin (Sigma) were selected on the basis of previous findings (43), showing >90% inhibition of protein synthesis in cortex for 2 h. Anisomycin was dissolved in a solution of 40% DMSO, brought to pH 7, and then diluted with 0.9% saline solution. The doses used in this experiment were 25, 50, and 100 μg per side.

Selective blockade of tPA activity was obtained through direct infusions into the VS of PAI-1 (Calbiochem). PAI-1 was dissolved in PBS solution and administered at the doses of 0.0625, 0.125, 0.25, and 0.5 μg per side. For a detailed description of the infusion procedure, see *SI Text*.

Behavioral Procedures. ***Spatial discrimination task.*** The task, which has been previously demonstrated to be sensitive to hippocampal lesions (44), consists of placing mice in an open field containing five objects and, after three sessions of habituation, examining their reactivity to object displacement. To distinguish between short- and long-term memory, two different the time intervals between the last training session (S4) and the discrimination test (S5) were used (3 min and 24 h, respectively; for detailed description of the apparatus and behavioral procedures, see *SI Text*).

Water maze task. The procedure consisted of three different phases: a familiarization phase, a training phase, and a probe test (45). To distinguish between short- and long-term memory in this case as well, different time intervals were used between the last training session and the probe test.

Two different versions of the water maze have been used. In the place version, several extramaze visual cues were attached to the walls surrounding the apparatus. Mice were required to navigate to the invisible platform using the spatial cues available in the room. The platform was always located in the same quadrant during training phases. In the cue version, all the distal visual cues were removed and a single proximal cue was present, a black-painted plastic ball (3 cm diameter) hanging 7 cm above the surface of the platform. The position of the platform and the ball changed across sessions to prevent animals from using spatial bias. During the probe test, the platform was removed, and the ball was located in the quadrant opposite to that used in the last training session (see *SI Text* for detailed description).

Immunoblotting. For the CREB experiment, ventral striatal punches taken from eight different mice were used for each experimental condition. The values reported in Fig. 1*C* are means of two independent experiments. For plasminogen, the Western immunoblot shown in Fig. 4*B* is representative of four experiments, and a pool of four VS (from two animals) was used for each experimental condition. The results were evaluated for statistical significance using the two-tailed Student *t* test. Differences were considered significant for $P < 0.05$. For detailed description of the immunoblot experiments, see *SI Text*.

ODNs Tissue Penetration Experiment. For details of the ODN tissue penetration experiment, see *SI Text*.

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1. McGaugh JL (1966) Time-dependent processes in memory storage. *Science* 153: 1351–1358.
2. Lamprecht R, LeDoux J (2004) Structural plasticity and memory. *Nat Rev Neurosci* 5: 45–54.
3. Malinow R, Malenka RC (2002) AMPA receptor trafficking and synaptic plasticity. *Annu Rev Neurosci* 25:103–126.
4. Lee HK, et al. (2003) Phosphorylation of the AMPA receptor GluR1 subunit is required for synaptic plasticity and retention of spatial memory. *Cell* 112:631–643.
5. Bozon B, Davis S, Laroche S (2002) Regulated transcription of the immediate-early gene Zif268: Mechanisms and gene dosage-dependent function in synaptic plasticity and memory formation. *Hippocampus* 12:570–577.
6. Balderas I, et al. (2008) The consolidation of object and context recognition memory involve different regions of the temporal lobe. *Learn Mem* 15:618–624.
7. Scoville WB, Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry* 20:11–21.
8. Corkin S (1968) Acquisition of motor skill after bilateral medial temporal-lobe excision. *Neuropsychologia* 6:225–264.
9. Moser MB, Trommald M, Andersen P (1994) An increase in dendritic spine density on hippocampal CA1 pyramidal cells following spatial learning in adult rats suggests the formation of new synapses. *Proc Natl Acad Sci USA* 91:12673–12675.
10. Guzowski JF, McGaugh JL (1997) Antisense oligodeoxynucleotide-mediated disruption of hippocampal cAMP response element binding protein levels impairs consolidation of memory for water maze training. *Proc Natl Acad Sci USA* 94:2693–2698.
11. Annett LE, McGregor A, Robbins TW (1989) The effects of ibotenic acid lesions of the nucleus accumbens on spatial learning and extinction in the rat. *Behav Brain Res* 31: 231–242.
12. Ferretti V, Sargolini F, Oliverio A, Mele A, Roullet P (2007) Effects of intra-accumbens NMDA and AMPA receptor antagonists on short-term spatial learning in the Morris water maze task. *Behav Brain Res* 179:43–49.
13. Madani R, et al. (1999) Enhanced hippocampal long-term potentiation and learning by increased neuronal expression of tissue-type plasminogen activator in transgenic mice. *EMBO J* 18:3007–3012.
14. Baranes D, et al. (1998) Tissue plasminogen activator contributes to the late phase of LTP and to synaptic growth in the hippocampal mossy fiber pathway. *Neuron* 21: 813–825.
15. Neuhoff H, Roeper J, Schweizer M (1999) Activity-dependent formation of perforated synapses in cultured hippocampal neurons. *Eur J Neurosci* 11:4241–4250.
16. Plow EF, Herren T, Redlitz A, Miles LA, Hoover-Plow JL (1995) The cell biology of the plasminogen system. *FASEB J* 9:939–945.
17. Mayer M (1990) Biochemical and biological aspects of the plasminogen activation system. *Clin Biochem* 23:197–211.
18. Endo A, et al. (1998) Proteolysis of highly polysialylated NCAM by the tissue plasminogen activator-plasmin system in rats. *Neurosci Lett* 246:37–40.
19. Nicole O, et al. (2001) The proteolytic activity of tissue-plasminogen activator enhances NMDA receptor-mediated signaling. *Nat Med* 7:59–64.
20. Samson AL, Medcalf RL (2006) Tissue-type plasminogen activator: A multifaceted modulator of neurotransmission and synaptic plasticity. *Neuron* 50:673–678.
21. Bourtchuladze R, et al. (1994) Deficient long-term memory in mice with a targeted mutation of the cAMP-responsive element-binding protein. *Cell* 79:59–68.
22. Kida S, et al. (2002) CREB required for the stability of new and reactivated fear memories. *Nat Neurosci* 5:348–355.
23. Brightwell JJ, Smith CA, Neve RL, Colombo PJ (2007) Long-term memory for place learning is facilitated by expression of cAMP response element-binding protein in the dorsal hippocampus. *Learn Mem* 14:195–199.
24. Naghdi N, Majlessi N, Bozorgmehr T (2003) The effects of anisomycin (a protein synthesis inhibitor) on spatial learning and memory in CA1 region of rats hippocampus. *Behav Brain Res* 139:69–73.
25. Barrientos RM, O'Reilly RC, Rudy JW (2002) Memory for context is impaired by injecting anisomycin into dorsal hippocampus following context exploration. *Behav Brain Res* 134:299–306.
26. Pizzorusso T, et al. (2002) Reactivation of ocular dominance plasticity in the adult visual cortex. *Science* 298:1248–1251.
27. Meighan SE, et al. (2006) Effects of extracellular matrix-degrading proteases matrix metalloproteinases 3 and 9 on spatial learning and synaptic plasticity. *J Neurochem* 96:1227–1241.
28. Huang YY, et al. (1996) Mice lacking the gene encoding tissue-type plasminogen activator show a selective interference with late-phase long-term potentiation in both Schaffer collateral and mossy fiber pathways. *Proc Natl Acad Sci USA* 93: 8699–8704.
29. Pawlak R, et al. (2002) Rapid, specific and active site-catalyzed effect of tissue-plasminogen activator on hippocampus-dependent learning in mice. *Neuroscience* 113:995–1001.
30. Centonze D, et al. (2002) Tissue plasminogen activator is required for corticostriatal long-term potentiation. *Eur J Neurosci* 16:713–721.
31. Frankland PW, Bontempi B (2005) The organization of recent and remote memories. *Nat Rev Neurosci* 6:119–130.
32. Moscovitch M, et al. (2005) Functional neuroanatomy of remote episodic, semantic and spatial memory: A unified account based on multiple trace theory. *J Anat* 207: 35–66.
33. Hoffman KL, McNaughton BL (2002) Sleep on it: Cortical reorganization after-the-fact. *Trends Neurosci* 25:1–2.
34. White NM, McDonald RJ (2002) Multiple parallel memory systems in the brain of the rat. *Neurobiol Learn Mem* 77:125–184.
35. Izquierdo I, et al. (2006) The connection between the hippocampal and the striatal memory systems of the brain: A review of recent findings. *Neurotox Res* 10:113–121.
36. Packard MG, Teather LA (1997) Double dissociation of hippocampal and dorsal-striatal memory systems by posttraining intracerebral injections of 2-amino-5-phosphonopentanoic acid. *Behav Neurosci* 111:543–551.
37. Packard MG (1999) Glutamate infused posttraining into the hippocampus or caudate-putamen differentially strengthens place and response learning. *Proc Natl Acad Sci USA* 96:12881–12886.
38. Mogenson GJ, Jones DL, Yim CY (1980) From motivation to action: Functional interface between the limbic system and the motor system. *Prog Neurobiol* 14:69–97.
39. Berke JD, Breck JT, Eichenbaum H (2009) Striatal versus hippocampal representations during win-stay maze performance. *J Neurophysiol* 101:1575–1587.
40. Rekart JL, Sandoval CJ, Bermudez-Rattoni F, Routtenberg A (2007) Remodeling of hippocampal mossy fibers is selectively induced seven days after the acquisition of a spatial but not a cued reference memory task. *Learn Mem* 14:416–421.
41. Pennartz CM, et al. (2009) Corticostriatal interactions during learning, memory processing, and decision making. *J Neurosci* 29:12831–12838.
42. Franklin BJ, Paxinos G (1997) The mouse brain in stereotaxic coordinates (Academic Press, San Diego).
43. Rosenblum K, Meiri N, Dudai Y (1993) Taste memory: The role of protein synthesis in gustatory cortex. *Behav Neural Biol* 59:49–56.
44. Sargolini F, Roullet P, Oliverio A, Mele A (1999) Effects of lesions to the glutamatergic afferents to the nucleus accumbens in the modulation of reactivity to spatial and non-spatial novelty in mice. *Neuroscience* 93:855–867.
45. Florian C, Roullet P (2004) Hippocampal CA3-region is crucial for acquisition and memory consolidation in Morris water maze task in mice. *Behav Brain Res* 154: 365–374.

Brain and Creativity

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Creativity can be considered from different points of view. A first possibility is to trace its natural history in mammals, mostly in non human primates. A second one is to consider mental processes, such as analogies, that may result in creative associations as evident in many fields, from arts to sciences. These two approaches lead to a better understanding of cognitive systems at the roots of creative behaviour. A third strategy relies on an analysis of primary and secondary states of mind characterizing flow and creativity. Flow, the mental state of operation in which a person is fully immersed in what he or she is doing, typical of intense problem solving activities, has been explained in terms of reduced prefrontal activity. While it is not difficult to carry out tests of problem solving activity, creativity is much more elusive and it is not easy to measure it. Thus, flow has often been simplistically assimilated to creativity and it has been assumed that also creative performance depends on low prefrontal activity. It is instead proposed that creativity involves two consecutive steps: 1. Generation of novelty, mostly in the ventral striatum. 2. Analysis of novelty by the prefrontal cortex that transforms it into creative behaviour. The emergence of creativity has been explained through a Darwinian process based upon the classic variation-selection procedure. Thus, basal ganglia, with their implicit strategies and memories, may be regarded as a mechanism that continuously generates novelty (variation) while the prefrontal cortex, possibly its dorsolateral areas, may be considered as the computational mechanism that transforms novelty (selection) into explicit creative behaviours.

§1. What is creativity?

Definitions of creativity are often unsatisfactory but in the most general terms they relay to attitudes, capacities and behaviours leading to some innovatory outcome. Creativity reflects an enhanced intensity of perception, cognition, and expression which occurs either spontaneously or is elicited by specific stimuli to relate and integrate variables not ordinarily associated with each other.[1)] Thus, when we refer to creative behaviours we also consider it in terms of a number of capacities which change and ripen during development and are characterized by a long natural history. As a matter of fact, creativity applies to a child that makes an innovatory use of a toy or of some amorphous material in order to adapt them to an alternative function, but also to an animal that solves a problem outside its usual stereotyped repertoire.

If we look at creativity from a broader point of view we can relate it to a number of functions and characteristics of our brain, namely its plasticity and ability to elaborate a plurality of mental schemes and visions of the world. Each mental function comprehends a number of plastic, creative facets: these are evident within perception, memory, mental imagery and representations of reality, during diurnal activities as well as dreaming. The origin of creativity depends on the gap existing between the real world and its mental representations: in fact, there are not facts or experiences that are represented straightforwardly, as to say without being in-

terpreted and screened through hypotheses corresponding to a theory, a vision of reality. If our brain just limited itself to register of information, to the formation of "neutral" memories through a computer-like process of categorization without diverging from strict rationality and from logic-computational strategies, there would be no room for plastic, divergent, creative mental processes. For example, the continuous reconstruction of memories, their re-consolidation,[2)–4)] their contamination caused by experiences occurring in succession, their conscious or unconscious reorganization belong to plastic, creative processes leading to a representation of reality that deviates from its initial core.

If we consider creativity in terms of its neural bases, a first classical approach refers to the different functions of the two cerebral hemispheres. From the one side we are endowed by logic-symbolic activities that mostly depend on language and therefore on the left side of our brain. From the other side, "holistic" activities lead to a strategy that also considers the ensemble of a number of facts, in particular emotional facts, and depends on the right hemisphere. Even if the characteristics of hemispheric functions are more variegated and less clear-cut, we cannot minimize the fact that the left half of our brain exerts a preponderant role in symbolic-linguistic activities, as to say in computational processes, a fact that is at the ground of those theories of mind that assimilate biological and artificial intelligence.

Many studies, mostly based on assessment through functional magnetic resonance, are centred on the asymmetric role of the two cerebral hemispheres. These studies suggest that creative solutions are associated to the fact that the left hemisphere is "switched off" while the right half of the brain is turned on: this state gives way to fluid associations, metaphors, analogies at the ground of new points of view, as to say of creativity.[5),6)]

The role of the right hemisphere in the discovery of a solution or of new explanations is emphasized by the fact that this hemisphere is involved in a number of functions such as musical perception and production, visual imagery and visual artistic creations, as indicated by Michael Gazzaniga.[7)] The same hemisphere is also implicated in the production of associations when verbal stimuli are used. It is well known that, due to the architecture of visual pathways, a visual stimulus (such as a written word) sent to the left visual field is processed by the right hemisphere while a visual stimulus sent to the right visual field is processed by the left hemisphere. Verbal stimuli processed by the right hemisphere result in a higher number of mental associations, and more specifically in richer associations and analogies, than stimuli processed by the left brain. By using functional magnetic resonance it has also been possible to indicate that the sudden discovery of the solution of a problem is a process that mostly involves the right hemisphere:[8),9)] more specifically, when the subjects discover the right answer in a test, the temporal lobe of their right hemisphere undergoes a quick activation. The activation of the right antero-superior temporal gyrus is preceded by a quick change of activity at the level of the prefrontal cortex, an area involved in a number of cognitive, executive and attentive tasks. This separation of hemispheric competencies often results in a notion of creativity in which right-brain functions are assimilated to creative, emotional, "instinctual" processes in antagonism to left-brain rationality and semantic, cognitive activities.[10)]

§2. A natural history of creativity

From an evolutionary point of view, creativity involves both the process and product of unprecedented or novel perception, thoughts, or actions by which an animal or a species copes with present or potential changes in the structure of its environment. In order to trace a possible natural history of creativity, as to say the evolutionary development of the creative potential of the brain and of its innovatory aptitude, we can start from the broad behavioural diversification evident among different animal species. There are species characterized by higher levels of behavioural rigidity, as to say by a trend towards stereotyped, scarcely variable responses which depend on instinctive mechanisms, and more plastic species in which an individual behavioural repertoire may be evident in response to environmental constraints or novelties.[11)] What are the advantages of these two conditions? In a homogeneous, slowly changing environment behavioural specialization is an advantage, though there is the risk that sudden changes do not result in adaptive mechanisms, a fact that may put at risk the survival of a species. From the other side, a non-specialized animal who relies on a broad number of behaviours organized through its individual experience, spends its entire life to solve those problems that are solved by the genetic patrimony of a specialized animal. While specialized species depend on instinctive patters determined by genetic memories, generalist species are more flexible, acquire new behavioural patterns through individual experience and are also able to temporarily assemble different behavioural patterns to solve new problems.

But what makes a species plastic and able to find new and creative solutions? The difference between specialized and non-specialized species does not depend on the level of cerebral complexity only. There are in fact other mechanisms resulting in behavioural variability such as varied diet, safety from predators and also living in a "relaxed" social context, a non agonistic environment allowing a "hedonistic attitude":[12)] freedom from predators and enemies favours strategies more plastic than those semi-automatic patterns set by instincts. Behavioural variability also depends on two important factors: dreaming and playing. As indicated by a large body of experiments, the REM (Rapid Eye Movements) sleep phase in which most of dreams occur has an important role in terms of shaping neural circuits. In human infancy dreaming activity is at its peak and during REM periods neural circuits are shaped through synaptic pruning and consolidation of those synapses involved in critical experiences.[13)] It is during the REM phase that memories are categorized and consolidated and that non relevant information is downloaded from neural networks.[14)] In addition to that, dreams are characterized by a sort of mental kaleidoscopic activity leading to a rich imagery and unconscious mental dynamics that do not generally take place during waking.

Play is a behavioural activity evident in higher mammals but almost absent in other species. During play brain activity is at its peak:[15)] in children, open air games involve a number of sensations, perceptions, emotions, movements and, most of all, a strong cognitive activity. One of the functions of play is to stimulate brain development and cognition: this explains why its role increases during infancy in light of a positive correlation between play and brain and cognitive growth.[16)–20)] In fact,

the developmental curves of play and brain growth overlap in all mammal species and reach their peak at pre-adolescence, a developmental phase characterized by increased synaptic connections, dendritic growth and myelinisation of a large number of nervous fibres resulting in increased functional brain capacity. Among other data, augmented c-FOS protein synthesis during play indicates that this activity has a positive neuronal trophic effect.[21)]

Obviously, a varied diet, safety from predators, a "hedonistic" environment, REM sleep and play are prerequisites but not synonymous of creativity. However, a variable and plastic behavioural repertoire may be considered as a precondition of creative behaviour. Different studies, mostly on primates, analyze factors leading to variable responses. One of the behavioural activities taken into consideration is the manipulation of non-edible objects. Glickman and Sroges,[22)] conducted a seminal study on more than 100 animal species, ranging from reptiles to non-human primates, in which they assessed reactivity –or curiosity– as measured by visual orientation towards a new object and its manipulation (number and type of body contacts with the object). Within primates, clear differences are evident in terms of both curiosity and object manipulation: gorillas, orang-utans or chimpanzees were the most exploratory, gibbons and macaques occupied an intermediate position while new world monkeys were characterized by a scarce body interaction with new objects. In general, anthropomorphic primates make contact with the object through a large number of body parts. They also make a large number of non-stereotyped movements in which the object is involved and make use of the object as a tool. Anthropomorphic primates also tend to innovate, are less repetitive, get easily tired of a movement already practiced or of a use of an object already known: despite that, they do not completely lose their interest in the object –for example a rope or a stick– and give birth to new behavioural patterns in a kind of recombination play. It is from this play that a novelty may suddenly emerge, thus being co-opted in the behavioural repertoire of the animal.[23)] In conclusion, the most meaningful behavioural innovation stemming from the large development of the associative cortex of anthropomorphic primates is the variety of actions and uses that an animal makes with an object. This eventually leads to sophisticated hunting strategies, cooperative behaviours and cultural transmission.

To sum up, anthropomorphic monkeys probe different possibilities and interactions with reality, through a mixture of exploration, curiosity and "analytic" attitudes deployed in a direct, concrete way. This attitude is not very different from that of a child playing with wood blocks, building different towers, exploring different combinations: the results of his play are often unpredictable and hardly separable from the hypotheses about the consequences of his own actions.

§3. The creative potential of analogies

A central aspect of creativity is the ability to combine and mix in a new way an already existing "capital", as to say to use the resources available as "bricks" to build new associations. As indicated by the mathematician Henry Poincaré,[24)] "To create means to make new combinations of useful associative items. Creative

ideas show relations between facts that are already known but that are erroneously believed to be unrelated to each other".

An important aspect of creativity is therefore the ability to pick up analogies between mental items that until a given moment do not seem to be associated. New ideas do not generally stem from deductive reasoning: on the contrary, very often ideas emerge from mental images. The use of analogies allows to grab similarities and relationships among objects, experiences and facts in order to fill a cognitive gap or to solve a problem through prior experience and knowledge. Analogies embody abstract concepts by building a mental model of a reality that otherwise cannot be easily represented since it is far from our senses. This strategy allows many informal artists to give body to concepts that would be otherwise difficult to translate. This embodiment of ideas that our senses do not seize, implies that our mind does not mirror a real world but artificially builds a new one.

Analogical thinking[25)] draws therefore from previous experiences and memories and generates new meanings. This approach, as indicated by Amabile,[26)] increases the possibility to lead to creative results. An approach only based upon logics and on its strict rules does not in fact leave much room to those playful associations that are possible when we abandon ourselves to imagination and reduce logic control. There are two cortical regions that are involved in the production of analogies, associative and prefrontal cortex, the latter being much expanded in humans in relation to other mammals and primates. As indicated by its name, associative cortex makes possible an association between different components of the same experience. For example, to know somebody means to memorize her face, voice, the context in which we met her, the emotional reactions involved such as sympathy, indifference, antipathy and so on. These different components of experience are distributed throughout a range of cortical territories and later re-associated thanks to the role of the associative cortex: this procedure generates again the fullness of a given memory. By starting from a single cue, for example the tone of the voice, the associative cortex restores the critical aspects of a face, the emotions involved and so on. The prefrontal cortex, may instead be considered as a sort of dynamic filter, a depository of representations where it is possible to select those items that are most critical in order to give an answer to a specific request. For example, if I ask somebody to tell me the colour of the air of his friend he will be able to answer also because other disturbing information, such as those related to the tone of his voice or to the environment in which we meet him, are blocked. If a person gets confused, he might react to the same question by answering that his friend has a very sharp tone of voice or that he is very agreeable.

When analogies are created, the prefrontal cortex selects the information while the associative cortex interconnects common items, by comparing for example blonde hair to a golden sunset, to gold etc. What is the structure of analogical thinking? In their simplest form analogies imply the transition from a source –or known matter– to a target or unknown matter. For example, when we face a new situation, such as a working problem or a new relationship with an unknown person, we make an automatic use of analogy, as to say our mind automatically searches for a previous situation which may be assimilated to the new one and proposes a solution in line with the previous way out. In a similar way, a scientist facing a new reality will try

to solve it by applying to the new context an analogy based on previous knowledge. Different types of logics play a role in the elaboration of an analogy. For example children will build up analogies on the ground of "magic" thoughts, typical of infancy, while adults or scientists will produce analogies that must be screened through logics in order to judge if they are plausible and useful.

Analogical thinking is not grounded on usual logic deductions: however it implies a form of logics (ana-logics) that leads to an understanding of an unknown reality though a series of constraints. It is necessary to proceed through these bottlenecks in order to configure an analogy useful to elaborate a map of the unknown target on the ground of known information. Thus analogies represent an experimental tool in order to afford new situations or to formulate new theories. James Maxwell, for example, made use of his knowledge of the properties of water waves in order to hypothesize the behaviour of sound waves when they hit a solid surface (such as it happens to sea waves when they hit a rock) or when they hit each other.

Obviously, grabbing new relationships may happen by chance if we just step into a source that fits the target, though this represents a rather exceptional event. For example, a lightning during a storm offered Benjamin Franklin, who was investigating the nature of electricity, an analogical model to explain the sparks produced by an electric discharge of two close conductors. But chance, as suggested by the great biologist Louis Pasteur, "supports the prepared mind". Though analogies are produced in an almost spontaneous way from our mind, their practice and elaboration may be of great help since they result in the activation of divergent and convergent procedures respectively depending on holistic and logic-rational strategies.[27] Different modalities and strategies for selectively increasing the production of analogies have been therefore described.[25]

§4. Implicit and explicit cognitive systems

As just indicated, one of the main characteristics of creative behaviour is the recombination of information in novel and potentially useful ways such as in analogical thinking. A critical approach to this cognitive strategy is therefore the study and description of underlying neural and cognitive systems.[28]

From an evolutionary point of view, the brain has developed two different types of neural systems, each designed to deal with a different kind of information, emotional or cognitive. Despite the overlapping between these two informational systems, when these pathways reach the thalamus two distinct ways are followed: initial processing of emotional content occurs in various limbic system structures such as the amygdala while the next levels of affective processing take place in the cingulate cortex and the ventromedial prefrontal cortex. On the contrary, the cognitive system involves another set of limbic structures, primarily the hippocampal formation, and the temporal, occipital, and parietal cortices. It is generally agreed that this circuit is the site of long-term memory storage.[29),30] Full integration of emotional and cognitive information depends on the fact that both types of computations, emotional and cognitive, converge back on the dorsolateral prefrontal cortex.[31] This cortex is involved in executive processes and integrates the information in order to allow

higher cognitive functions such abstract thinking, cognitive flexibility, planning, self-reflective consciousness.[32] It is also at the level of the dorsolateral prefrontal cortex that plans and strategies for appropriate behaviour are formulated and put to action through the motor cortices. Functions such as working memory,[33] temporal integration[34] and sustained and selective attention[35] also depend on this cortical area and allow complex cognitive functions to take place.

In addition to these two different types of knowledge (emotional or cognitive), there are two different systems involved in the acquisition, memorization and cognitive representation, the explicit and the implicit systems. The explicit system is rule-based and its content can be verbally expressed: in addition to that, it is tied to conscious awareness. The implicit system is skill or experience-based, its content can not be verbally expressed, but only through task performance, and it is inaccessible to conscious awareness.[36,37] From a neural point of view, the explicit system is associated to the higher cognitive functions of the frontal and prefrontal lobes and medial temporal lobe structures. This system has evolved to increase cognitive flexibility. In contrast, the implicit system is associated to the skill-based knowledge supported primarily by the basal ganglia and has the advantage of being more efficient. The evolutionary origin of prefrontal cortex and of the explicit system is rather recent and therefore typical of those primates with a highly developed prefrontal cortex. This fact supports a hierarchical view of information processing where the most sophisticated mental abilities, and thus explicit knowledge representation, depend on the highest-order structure, the prefrontal cortex.[38] However, it would be simplifying to definitely separate explicit and implicit knowledge and the nervous structures upon which these two cognitive abilities depend. First, both systems may be activated in parallel.[39] Second, the striatum, one of the main structures of basal ganglia, is also involved in explicit cognitive functions and may be tuned with prefrontal cortex cognitive functions, also due to the complex connections associating the striatum to the frontal/prefrontal cortex. In addition, the striatum combines information from different cortical areas since their respective terminal fields converge.[40]

The function of ventral striatum emerges from a body of recent research indicating that the accumbens exerts a central role in behaviours, either positively or negatively reinforced.[41] Reinforcement may be concrete but also immaterial or virtual, mostly in human beings whose learning depends on internalized reinforcements such as parental or adult's approval of appropriate child behaviour. In addition to that, the accumbens, has a role in both procedural (implicit) and declarative (explicit) memories,[42] including those semantic memories which are mostly based upon language. The accumbens represents a key node of a network receiving critical (emotional) information from limbic structures such as the amygdala, from the mesencephalic nuclei involved in reinforced behaviours, from cognitive structures such as the hippocampus and the prefrontal cortex. This complex network, where the accumbens receives inputs and sends information to the other nuclei and cortical structures, explains the ideal position of this nucleus to elaborate and convert information in appropriate behavioural responses that may eventually be reinforced. In addition to that, the ventral striatum anticipates the rewarding outcomes of choices and signals the negative outcomes of those behaviours and decisions that are expected

to be rewarded. It has been suggested that stimuli detected in a novel context or out of expected context activate the ventral striatum, as the basal ganglia monitor the reliability of predictions made in the prefrontal cortex.[43] Expectations may be cognitive as well as motor and since the chemical signals of the stress response are evoked by even mild dissonance such as discrepancies between perceptions and expectations,[44] it is reasonable, as suggested by Greenberg,[45] that the basal ganglia are deeply involved. The ventral striatum is also responsible for commuting from one task to another, depending on the needs of the moment. In other words, through this procedure it is possible to adapt a cognitive strategy to environmental requirements. Thus, the subcortical mechanisms of reinforcement, through their interaction with the frontal cortex and the emotional limbic and striatal systems, exert a key function in executive tasks such as planning, the selection of the appropriate action or, in other words, in decisional processes.

In summary, the hippocampus, temporal cortex and frontal structures are involved in learning new experiences, mostly based on explicit memory while the striatal system takes charge of the same information when it gets more known and recurs though time.[46] The circuits responsible for explicit and implicit cognitive functions (the hippocampus-cortex and the basal ganglia) may also act in parallel in many instances or take charge of the same task depending on factors such as novelty, practice, habits.

Having clarified the role of different brain structures in relation to implicit and explicit experiences, memory, learning and a number of executive functions we may proceed to an analysis of those neural changes that are associated to problem solving, flow (the mental state in which the person is fully immersed, typical of intense problem solving activities) and creativity in terms of primary and secondary processes.

§5. Primary and secondary processes of thought

It is well known that the brain frontal cortex undergoes different levels of activity or vigilance: sleepiness, for example, is associated to a low level of vigilance while playing a videogame or responding to sudden stimuli in short time requires high levels of cortical activation. The highest levels are reached in the course of emotions such as rage, fear etc. When learning is concerned, the optimal performance is reached at intermediate activation levels: while easy tasks are performed even at relatively high levels, complex tasks require lower levels. In other words, in order to perform an easy task we may be a little excited while to reach a higher concentration the brain must attain a lower activation level. During the transition from waking to reverie (open eyes dreams) and finally to full sleep the level of vigilance decreases: EEG waves become more and more slower while their voltage increases. Primary processes of thought –such as free associations and reverie-from which analogies and creative ideas might emerge– take place at intermediate levels of activation while secondary processes (in which cognition is abstract, logical and reality-oriented) involve attention and take place at levels of higher activation.[47] It has been suggested that prefrontal cortex activation leads to a block of "irrelevant" behaviours, a fact that increases purpose-oriented behaviour, such as problem solving, without paying

attention to irrelevant mental associations.

Fromm[48] suggested that the primary process-secondary process continuum should be the main dimension along which cognition varies and proposed that creative individuals should be better able to alternate between these two thought dimensions than uncreative people.[49] According to this hypothesis, creative inspiration should involve a regression to a primary process state of consciousness. While primary process cognition is associative and should facilitate the discovery of new combinations of elements, creative elaboration should instead require the return to a secondary process state. Different data support the hypotheses that creative people have easier access to primary processes modes of thought.[50] For example, writing becomes more conventional and stereotyped in conditions of higher activation[51] and stress results in decreased originality when associative tests are performed.

In conclusion, the studies reviewed up to here imply that discovery of a solution (which is often improperly fully assimilated to creative behaviour) is characterized by the ability to commute from secondary to primary processes, thus letting emerge free associations and analogies. While one can agree on the fact that search of new solutions is related to an ability to switch off the prefrontal cortex, as to say to commute from secondary to primary thought processes, it seems less possible that what has been called a state of "hypofrontality"[52] or reduced prefrontal cortex activity leads to creativity. At this point a distinction should be done between flow, and creativity. As we will see, flow, the mental state in which the person is fully immersed in what he or she is doing, is typical of intense problem solving activities[53] and has been correlated to reduced prefrontal activity. Over creativity, flow has the advantage to allow different experimental approaches resulting in its measure and neural correlations. Creativity, on the contrary, is much more elusive and it is not easy to measure it. Thus flow has often been simplistically assimilated to creativity and it has been assumed that also creative activities depend on low prefrontal activity.

Thus, in the next section a distinction will be carried out between flow and creativity with the aim of differentiating the neural processes at the ground of these two mental functions.

§6. Flow and creativity

Flow is a mental state characterized by a feeling of energized focus, full involvement, and success in the process of the activity. Proposed by psychologist Mihaly Csikszentmihalyi,[53] the concept has been widely referenced across a variety of fields but has at its ground "an almost automatic, effortless, yet highly focused state of consciousness".[53]

A flow state ensues when one becomes so deeply focused on a task and follows it with such passion that everything else disappears. Flow is often associated to an euphoric state, in which the task is performed, without strain or effort, to the best of the person's ability. According to Csikszentmihalyi, any activity, mental or physical, can produce flow as long as it is a challenging task that demands intense concentration and commitment, contains clear goals, provides immediate feedback,

and is perfectly matched to the person's skill level. The fact that people feel they operate without conscious thinking suggests that the prefrontal cortex is not an essential feature in flow processes and that flow may be considered as a fruit of implicit cognitive systems.[54)]

As previously noted, the explicit system is associated with the cognitive functions of the frontal lobe and medial temporal lobe and is responsible for increased cognitive flexibility. The implicit system is instead associated with the skill-based knowledge: it depends on basal ganglia and has the advantage of being more efficient. Thus, the flow state may be considered as a period during which a highly practiced skill or cognitive function that is already represented in the implicit system's knowledge base is realized without interference from the explicit system.[54)] The experience of flow may therefore be considered in terms of a state of transient lower activity of the prefrontal lobe that enables the temporary suppression of the analytical capacities of the explicit system.

In the course of flow, concentration is focused on a target, a fact that seems to challenge a state of decreased activity of the frontal lobe. Flow, in fact, demands attention to be directed and persistent, thus suggesting that the frontal attentional network should be active. However, focused attention is also a feature of other states of altered consciousness implying transient hypofrontality. In addition to that, people in a state of flow report a state that is consistent with decreased prefrontal function, such as the disappearance of self-consciousness and no distractions. Thus, flow is generally considered as a state of lower frontal activity with the notable exception of executive attention enabling the mind to be focused on a target by switching off other executive, cognitive abilities of the prefrontal cortex:[55),56)] focusing attention on the current task allows the implicit system to execute it at maximum skill level and efficiency. Creativity, on the contrary, emerges from the engagement of different brain circuits: novelty is first generated within the implicit system, namely the ventral striatum, and then analyzed by the prefrontal cortex that transforms novelty into creative responses and behaviours. As a matter of fact, it has been shown by different studies that the striatal implicit system reacts to novelty and generates novel responses in order to cope with environmental changes.[57)−59)] Brain imaging studies also show that in humans the striatum generates new and appropriate behaviours in response to changing situations.[60)] Subsequently, the prefrontal cortex takes charge of newly acquired behaviours but as they turn into repetitive practice are managed again by the basal ganglia, as to say transformed into implicit procedures.

Simonton[61)] equates creativity to a Darwinian process based upon the classic procedure variation-selection. In this regard, the basal ganglia, with their implicit strategies and memories, may be regarded as an mechanism that continuously produces novelty[62)] while the prefrontal cortex, possibly its dorsolateral areas, is the computational mechanism that transforms novelty into creative behaviours. Thus, the rich associative network that allows the striatum to merge motivational, emotional and cognitive information from different cortical areas and to relay it to the prefrontal cortex represents a generative tool that can explain the creative explorative behaviour of non-human primates, the transformation of play motor and exploratory experiences into cognitive patterns and the production of analogies at the ground of

creative discoveries and approaches.

In conclusion, as our knowledge of the brain increases, it is more and more evident that a cognitive function often depends on a multiplicity and redundancy of mechanisms instead on a single structure or system. For example, language does not exclusively stem from motor and sensory areas on the left hemisphere but also from the networks connecting these areas to the basal ganglia.[63] Similarly, the analysis of creativity shows that a plurality of structures and functions are implicated in its occurrence and that the traditional duality between right and left hemispheric functions cannot per se explain creative behaviours. While many theories of creativity still adhere to this simplistic view, it is today evident that this faculty must be considered within the framework of its several relationships with our neural and cognitive processes such as implicit and explicit strategies, primary and secondary states of mind, executive abilities, purpose-oriented behaviours and emotionality. In addition to that, creativity may also be regarded from a more general point of view, as to say in terms of those plastic processes that allow to cope with the environment and to adapt to it through new, original strategies: in evolutionary terms these processes involve the passage from specialized, stereotyped behaviours to generalist approaches and to novelty-seeking behaviour. As a consequence of these multifaceted relations between brain and creativity we should keep in mind that inventive and original attitudes may be enhanced during infancy by encouraging a multiplicity of activities which are the preconditions of creative behaviours, such as free and social play, analogical thinking, focused attention.[64]

References

1) N. Greenberg, in *The Neuroethology of Paul MacLean: Frontiers and Convergences*, ed. G. Cory and R. Gardner (Praeger, London, 2002), p. 45.
2) D. J. Lewis, Psychological Bulletin **86** (1979), 1054.
3) K. Nader, Trends in Neuroscience **26** (2003), 65.
4) S. J. Sara, Learning and Memory **7** (2000), 73.
5) J. Levy, in *Beauty and the Brain*, ed. F. I. Rentschler, B. Herzberger and D. Epstein, (Birkhauser Verlag, Basel, 1988).
6) C. Martindale in *Handbook of creativity*, ed. R. J. Sternberg (Cambridge University Press, Cambridge, 1999), p. 137.
7) M. S. Gazzaniga and S. A. Hillyard, Neuropsychologia **9** (1971), 273.
8) M. J. Beeman and E. M. Bowden, Memory and Cognition **28** (2000), 1231.
9) S. M. Fiore and J. W. Schooler, in *Right hemisphere language comprehension*, ed. M. Beeman and C. Chiarello (Erlbaum, Mahwah, NJ, 1998), p. 349.
10) R. B. Ivry and L. C. Robertson, *The two sides of perception* (MIT Press, Cambridge, MA, 1988).
11) A. Oliverio, in *Neurobiological Basis of Learning and Memory*, ed. Y. Tsukada and B. W. Agranoff (J. Wiley, New York, 1980), p. 193.
12) A. Oliverio, *Storia naturale della mente: l'evoluzione del comportamento* (Boringhieri, Turin, 1984).
13) R. Adair and H. Bauchner, Current Problem in Pediatrics **23** (1993), 147.
14) G. Tononi and C. Cirelli, Sleep Medicine Reviews **10** (2006), 49.
15) G. M. Burghardt, in *Handbook of Behavioral Neurobiology*, ed. E. Blass (Plenum Press, New York, 2001), p. 317.
    G. M. Burghardt, Evolution and Cognition **5** (1999), 115.
16) K. P. Lewis and R. A. Barton, Human Nature **15** (2004), 5.
17) B. D. Perry, R. Pollard, T. Blakely, W. Baker and D. Vigilante, Infant. Mental. Health. J. **16** (1995), 271.

18) A. D. Pellegrini and P. K. Smith, Child Psychology and Psychiatry Review **3** (1998), 51.
19) Ed. J. P. Shonkoff and D. A. Phillips, *From Neurons to Neighborhoods:The Science of Early Childhood Development* (Academy Press, Washington, DC, 2000).
20) C. S. Tamis-LeMonda, J. D. Shannon, N. J. Cabrera and M. E. Lamb, Child Development **75** (2004), 1806.
21) S. M. Siviy, S. Huguenin, L. A. Kerrigan, S. J. Kuhlman, S. W. James and K. Hiraizumi, Society for Neuroscience Abstracts **19** (1994), 161.
22) S. E. Glickman and R. W. Sroges, Behaviour **26** (1966), 151.
23) D. F. Lancy, Annu. Rev. Anthropology **9** (1980), 471.
24) H. Poincaré, *The foundations of science* (Science Press, Lancaster, 1913), p. 115.
25) K. J. Holyoak and P. Thagard, *Mental leaps: Analogy in creative thought* (MIT Press, Cambridge, 1995).
26) T. Amabile, *The social psychology of creativity* (Springer Verlag, New York, 1983).
27) A. Oliverio, *L'arte di pensare, Rizzoli, Milan*, (1997), Japanese translation: *Ronriteki shikou no gijyutsu* (Daiwa Shobo, Tokyo, 2003).
28) A. Oliverio, *Come nasce un'idea. Intelligenza, creatività genio nell'era della distrazione* (Rizzoli, Milan, 2006).
29) P. F. C. Gilbert, Cognitive Brain Research **12** (2001), 61.
30) E. R. Kandel, J. H. Schwartza and T. M. Jessell, *Principles of Neuroscience* (Elsevier, New York, 1995).
31) J. M. Fuster, Psychobiology **28** (2000), 125.
32) A. Dietrich, Consciousness and Cognition **13** (2004), 746.
33) A. Baddeley, Quarterly J. Experimental Psychology A **49** (1996), 5.
34) J. M. Fuster, Ann. NY Acad. Sci. **769** (1995), 163.
35) M. Sarter, B. Givens and J. P. Bruno, Brain Research Reviews **35** (2001), 146.
36) Z. Dienes and J. A. Perner, Behavioural and Brain Sciences **5** (1999), 735.
37) D. L. Schacter, J. Experimental Psychology: Learning, Memory and Cognition **113** (1987), 501.
38) A. Dietrich, Consciousness and Cognition **12** (2003), 231.
39) M. G. Packard and J. L. McGaugh, Neurobiology of Learning and Memory **65** (1996), 65.
40) A. Parent and L. N. Hazrati, Brain Research Reviews **20** (1995), 91.
41) E. De Leonibus, A. Oliverio and A. Mele, Learning and Memory **12** (2005), 491.
42) A. Mele, M. Avena, P. Roullet, E. De Leonibus, S. Mandillo, F. Sargolini, R. Coccurello and A. Oliverio, Behavioral Pharmacology **15** (2004), 423.
43) R. M. J. Cotterill, Prog. in Neurobiology **64** (2001), 1.
44) D. S. Goldstein, Biofeedback and Self-Regulation **15** (1990), 243.
45) N. Greenberg, in *The Neuroethology of Paul MacLean: Frontiers and Convergences*, ed. G. Cory and R. Gardner (Praeger, London, 2002), p. 45.
46) R. A. Poldrack, J. Clark, J. Pare-Blagoev, D. Shohamy and J. Creso Moyano, Nature **414** (2001), 546.
47) C. Martindale, in *Handbook of creativity*, ed. R. J. Sternberg (Cambridge University Press, Cambridge, 1999), p. 137.
48) E. Fromm, J. Alteresd States of Consciousness **4** (1978), 115.
49) E. Kris, *Psychoanalytic explorations in art* (International University Press, New York, 1952).
50) M. A. Runco and S. O. Sakamoto, in *Handbook of creativity*, ed. R. J. Sternberg (Cambridge Univesrity Press, Cambridge, 1999), p. 62.
51) M. Jung-Beeman, E. M. Bowden, J. Haberman, J. L. Frymiare, S. Arambel-Liu, R. Greenblatt, P. J. Reber and J. Kounios, PLoS Biol. **2e97** (2004).
52) A. Dietrich, Consciousness and Cognition **12** (2003), 231.
53) M. Csikszentmihalyi, *Creativity: Flow and the Psychology of Discovery and Invention* (Harper Perennial, New York, 1996).
54) A. Dietrich, Consciousness and Cognition **13** (2004), 746.
55) Ed. M. I. Posner, *Cognitive Neuroscience of Attention* (Guilford, New York, 2004).
56) M. R. Rueda, M. K. Rothbart, L. Saccamanno and M. I. Posner, Proc. US Natl Acad. Sci. **102** (2005), 14931.
57) W. Caan, D. I. Perrett and E. T. Rolls, Brain Research **290** (1984), 53.
58) E. De Leonibus, A. Oliverio and A. Mele, Learning and Memory **12** (2005), 491.

59) R. Coccurello, W. Adriani, A. Oliverio and A. Mele, Psychopharmacology **152** (2000), 189.
60) K. M. Shafritz, P. Kartheiser and A. Belger, Neuroimage **25** (2005), 600.
61) D. K. Simonton, Psychological Bulletin **129** (2003), 475.
62) A. M. Graybiel, Schizophrenia Bulletin **23** (1997), 459.
63) P. Lieberman, Yearbook of Physical Anthropology **45** (2002), 36.
64) A. Oliverio, Das Kind **41** (2007), 51.