Le Professeur Avinoam B. Safran : Que fait-il aujourd'hui ?

Was macht eigentlich Prof. Dr. Avinoam B. Safran?

Hannes Wildberger, Zurich

Avinoam Safran fut Professeur d'ophtalmologie et Chef du service d'ophtalmologie aux Hôpitaux universitaires de Genève, de 1998 à 2010. Depuis qu'il est devenu émérite à Genève, il a été appelé à occuper une fonction de Professeur associé à Paris, à Sorbonne-Universités UPMC. Il y a un peu plus d'un an, l'auteur de ces lignes a rencontré Avinoam à Genève, pour discuter avec lui de ce qui s'est passé toutes ces années, et de ses projets actuels (Fig. 1).

Nous avons gardé en mémoire les événements scientifiques marquants qui se sont déroulés à Genève du temps d'Avinoam, et en particulier le congrès de l'International Neuro-Ophthalmology Society (INOS) en 2004, ou encore le cours de l'European University Professors of Ophthalmology (EUPO), en 2005. Le point culminant de ces rencontres fut sans doute le XVe congrès de INOS où, sous l'égide d'un éminent comité scientifique international, fut réuni le nombre alors le plus important de neuro-ophalmologues jamais venus du monde entier. On se souvient de l'émouvante attribution symbolique des noms de chercheurs ou citoyens célèbres de la République de Genève, chacun à une séance scientifique, et l'évocation de leurs réalisations: Georges de Morsier, Louis Albert Necker, Charles Bonnet, Henry Dunant, Otto Loewenstein, Léon Revilliod et Adolphe Francheschetti.

Avinoam Safran maîtrisait – et maîtrise toujours – une foule de détails scientifiques extraordinaires, des trésors de la sagesse. Il était toujours en quelque sorte le philosophe de l'intellect absolu du monde ophtalmologique en Suisse. Avinoam est un adversaire des simplifications outrancières, et un partisan des explications précises. Il sied de trouver le juste milieu entre les extrêmes, tout en assurant une profondeur nécessaire à la réflexion. Connaître et expliquer les détails est primordial, d'autant que nos patients ont tendance à nous détailler leurs plaintes, et sont bien rarement en mesure de nous présenter leurs symptômes de manière synthétique.

Fig. 1 Avinoam Safran, lors de notre entrevue de 2016.

Les recherches qu'Avinoam avait menées à Genève furent – entre autres – consacrées à la compensation fonctionnelle des déficits organiques du système visuel, réalisée par les processus de plasticité cérébrale.[1–7] Ces observations étaient souvent publiées en collaboration avec Theodor Landis, du Service de neurologie des HUG.

Le phénomène perceptif de « filling-in » (ou « complétion ») a fait l'objet d'études particulièrement approfondies. Les scotomes ne sont pas perçus par le patient lui-même comme des « trous » dans le champ visuel.[2] De ce fait, l'appréciation du champ visuel par le patient sur un fond structuré (une grille d'Amsler, par exemple) peut être trompeuse, alors qu'à l'inverse la périmétrie fine par projection de stimulus doit permettre de cerner correctement le déficit. C'est pour cette même raison que la tache aveugle physiologique (qui correspond à la papille optique) n'est jamais perçue spontanément.

Diverses situations particulières ont encore été décrites, comme celles du « thin man phenomenon »,[6] la distorsion spatiale induite par la présence d'un déficit du champ visuel.[7]

Dans la même perspective, Avinoam avait redéfini la réorganisation de la coordination sensori-motrices dans diverses formes de déficits visuels, en particulier les stratégies de lecture.[8–12] Il avait piloté un projet de développement d'implants rétiniens, en collaboration avec le Professeur J.-A. Sahel de Paris et l'EPFL,[13] et de psychophysique visuelle des implants rétiniens.[14–17]

C'est dans le cadre de son projet qu'en 2008, le Dr Joel Salzmann a réalisé dans le service d'ophtalmologie de Genève, la première implantation chirurgicale en Europe d'une prothèse rétinienne Argus II®.

En 2004, Safran a édité le Rapport de la Société française d'Ophtalmologie, sur la Neuro-ophtalmologie,[18] un ouvrage devenu une importante référence de la collection des Rapports de la Société (il peut être téléchargé sur internet), ainsi que d'autres ouvrages, sur « les dimensions de la douleur en ophtalmologie »[19] et la physiopathologie du handicap visuel et sa réadaptation.[20,21]

Depuis 2010 et qu'il a été nommé à Paris, Avinoam conduit des recherches à l'Institut de la Vision (INSERM) du Professeur José-Alain Sahel, où il dirige des thèses de neurosciences. Il consulte par ailleurs au Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts. Il prodigue enfin un enseignement de neuro-ophtalmologie et de neurosciences visuelles, et a entre autres été invité à faire des exposés au Collège de France.

Ses travaux de recherche sont consacrés aux transformations cérébrales provoquées par une perte de vision, en particulier la présence d'un scotome central (dans la maladie de Stargardt), d'une perte du champ périphérique (dans la rétinite pigmentaire), ou lors d'une cécité totale. Ces études portent sur trois niveaux: (1) les anomalies perceptives de la vision résiduelle ou dans les autres modalités sensorielles,[22,23] (2) la coordination transformée

entre information sensorielle résiduelle et le contrôle moteur,[24,25] et (3) la réorganisation des structures cérébrales, explorées par IRM structurelle et fonctionnelle.[26,27] Par ailleurs, Avinoam étudie l'importance neuroscientifique des œuvres d'art plastique, pour l'exploration de la fonction visuelle à l'état sain ou dans la maladie.[28]
Lors de mes récents échanges avec Avinoam, nous avons passé du français à l'anglais quand nous avons abordé les thèmes de recherche, et c'est pourquoi je poursuis ici aussi en anglais, pour être précis dans leur formulation.

1. Visual synesthesia: an insight into cerebral processing of vision and consciousness. Unanticipated perceptual phenomena following visual loss.

Cerebral plasticity provoked by visual loss results in unexpected, commonly misinterpreted sensorial experiences. Avinoam Safran and his colleagues explored the phenomenology and underlying mechanisms of so-called synesthetic percepts in blind individuals.[26,27]
Synesthesia can be defined as an extraordinary perceptual phenomenon, in which individuals experience unusual percepts elicited by the activation of an *unrelated* sensory modality or by a cognitive process.[27] For example, an affected person ‹sees› lightings and even ‹perceives› visual shapes when hearing sounds or performing a mathematical operation. Features of the synesthetic phenomena however vary from person to person.[27]
Acquired auditory-visual synesthesia was described more than 35 years ago in patients with optic nerve disorders.[29] Sudden short, sharp sounds of different origin such as cracklings of a cooling down television set after turning off were able to produce short visual sensations (photisms), in a variety of individual patterns. The photisms appeared within the range of scotomata and were considered a symptom of deafferentation in the lateral geniculate nucleus, sounds becoming able to induce inputs into the this nucleus.
Investigating manifestations of synesthesia in blindness, Safran's team redefined mechanisms involved. They clarified the role of proprioception in the induction of such inaccurate visual percept, resulting in unexpected perception of own hands when waving them.[26,27]
In a comprehensive review article by Safran et al.,[27] features differentiating genetic[30] from acquired types of synesthesia, their cerebral underlying mechanisms as well as their major, fascinating importance in society throughout history were reconsidered (Fig. 2). They emphasized that, most interestingly, synesthetes' prevalence among artists appears much higher as in fine art students where it was estimated to be 27 %.[31]
Reportedly, while Vincent van Gogh was taking piano lessons, his teacher noticed that he was continually relating the sounds of the piano keys with specific colors; considering then that his student was insane, the teacher sent him away.[32] Wassily Kandinsky's nonfigurative paintings (Fig. 3) and theory of synesthesia,[33] prompted by his own experience of extraordinary visions of lines and colours elicited by the sound of musical instruments, paved the way to abstract art and became a turning point in art history.

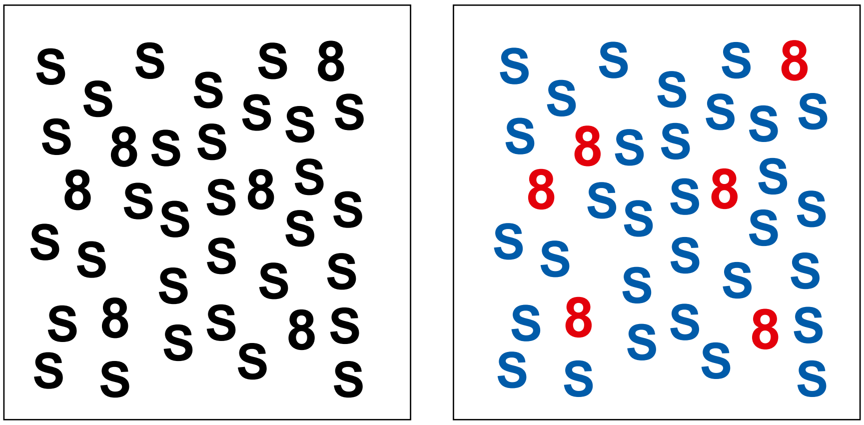

Fig. 2 Left: A set of black numbers. Right: The same set as perceived by a synesthete experiencing grapheme-colour synesthesia, the most common form of the condition; adapted from [23] and Ramachandran VS, Hubbard EM. Hearing colors, tasting shapes. Sci Am 2003; 288:52–59.

Safran also showed that Marc Chagall's consistent green or blue depiction of the faces of loved characters reflects a form of personality-color synesthesia,[27] as in some personality-color types of the condition, viewing known faces elicits emotionally mediated colour percepts, presenting either as coloured faces or coloured auras around heads.
Beside painters, the list of prominent persons with probable developmental synesthesia[34] includes Duke Ellington and Bob Dylan, but also Eugen Bleuler, the famous psychiatrist from Zurich, and Friedrich Nietzsche.
MRI studies conducted in synesthetes suggest that affected individuals show hyperconnectivity between cortical areas.[35] Synesthesia, like other illusory percepts, incite us to revisit the definition of visual consciousness.[27]

Value of artworks for the understanding of cerebral disorders. The rare neurological condition of the painter Francis Bacon, and the importance of its depiction.

Paintings by Francis Bacon (1909–1992) generated an astonishing interest in artistic circles, where he is celebrated as ‹one of the most enigmatic creative geniuses of the twentieth century›.[36] Recently the Sheikha Mayassa of Quatar`s royal family purchased a Bacon's triptych (a triple painting) for the incredible amount of 142 million (!) US dollars. The faces represented by Bacon are characteristically distorted and frightful (Fig. 4), but their significance is not understood.
Art critic Peppiatt states that they ‹challenge interpretation and provoke controversy›.[36] Bacon suffered numerous head traumata and exhibited a tormented mind. Was he toxic manic, psychopathic? Do misaligned eyes in portraits represent forms of skew deviation?
The well-known neurophysiologist Semir Zeki and Ishizu discussed the emotional effect *(‹the visual shock›)* caused by Bacon's distorted paintings on the viewers, and they reviewed cerebral mechanisms involved in face processing; but surprisingly they do not consider the possibility that the artist's brain was ill …[7]
Avinoam Safran was struck by apparently neurological features in defects of faces depicted by Bacon. Prompted by this observation, he thoroughly reviewed with colleagues[28,38] Bacon's published inter- ➜

views, and found that Bacon actually described particular perceptual experiences that clearly demonstrated he suffered a rare, mainly left occipital condition named dysmorphopsia[39] or central metamorphopsia.[40] Bacon's statements included the following:[28]

‹When I am watching you talking – I don't know what it is – I see a kind of image, which constantly changes: the movement of your mouth, of the head, somehow; it keeps changing all the time. I attempted to trap this thing in the portraits.›

Amazingly, Bacon's explicit description of his perceptual disorder had never caught the attention of art critics! The artist also provides clinical neuroscientists with most informative descriptions of visual percepts experienced during dysmorphopic episodes.[28]

2. Reorganization of coordination between residual sensory information and motor control following sectorial visual deficits. Visuo-motor coordination in blind people fitted with an Argus II® retinal prosthesis.

Peripheral field loss impairs interaction with the environment,[41] by altering spatial and own-body representation. The team of Avinoam Safran,[25] in collaboration with Professor Alain Berthoz from the Collège de France, investigated the effects of retinitis pigmentosa on patients' behaviour, using a high-tech device (VICON®) assessing both visual and whole body movements.

A variety of alterations were identified, including forward tilting of the head, frequent fixations of the ground (even knowing no obstacle was present), a peculiar alternating door edges fixation strategy before getting through a gate, and a peculiar strategy in rapid eye movements' generation. These adaptive features allowed better detection of changes in spatial configuration, collecting information for self-motion, updating postural reference frame and egocentric distances to environmental objects.[25] These mechanisms are of significant importance for the design rehabilitation procedures, and the development of optimized devices for visual substitution and restitution (e.g. using retinal prostheses).

With his neuroscience PhD students, Avinoam Safran[24] also analysed the visual search difficulties experienced by blind individuals fitted with an Argus II® camera-connected, epiretinal retinal prosthesis. These devices are susceptible to generate a dissociation between the orientation of the eyes and that of the head-mounted camera, and consequently induce a disturbance in spatial localization of produced visualized images.

Indeed, epiretinal prosthetic devices process images produced by the camera, and depend on camera (i. e., head) orientation; in contrast, brain mechanisms involved in spatial localization as a rule depend on gaze direction, based on efference copy which takes into account the message generated by the cerebral command to modify gaze direction, contribute to perceptual localization of the image.[42] The present study has shown that misalignments between gaze and head-mounted camera directions unavoidably occurred during visual search, as they cannot be volitionally prevented during performance of vestibulo-ocular reflexes, generating an illusion of a visual target movement, affecting visuo-motor coordination.

Interestingly, this investigation also found that after several years of regular use of the prosthetic device, cerebral mechanisms of fitted subjects developed compensatory strategies that partially minimize these difficulties.[24]

Fig. 3 Wassily Kandinsky (1866 – 1944): Improvisation Deluge, 1913, Lenbachhaus München. Kandinsky was presumed to be a colour synesthete.

3. The concept of brain connectivity. Cerebral reorganization following visual loss, according to the type of defect.

Neurons and neural populations do not function as islands onto themselves. Rather, they interact with other such elements through their afferent and efferent connections in an orchestrated manner so as to enable different sensorimotor and cognitive tasks to be performed.[43] Brodmann`s areas may represent anatomic places with a specific function.[44] In contrast, brain connectivity refers to a pattern of anatomical links («anatomical connectivity»), of statistical dependencies («functional connectivity») or of causal interactions («effective connectivity») between distinct units within a nervous system.[45]

Anatomical (structural) connectivity may be provided by diffusion weighted MRI (DWI). Functional neuroimaging methods, especially PET and fMRI, have been used extensively to evaluate the functional connectivity between different brain regions.[43]

Brain functional connectivity (FC) refers to inter-regional time-related synchrony of low frequency fluctuations in blood oxygenation level dependent functional MRI (fMRI).[46] The «resting state» of the brain or «task-based» applications are used, the latter during performance of an area-specific job. Brain connectivity datasets comprise networks of brain regions connected by anatomical tracts or by functional associations. Complex network analysis – a new multidisciplinary approach to the study of complex systems – aims to characterize these brain networks with a small number of neurobiologically meaningful and easily computable measures.[43,45]

Defects or organic isolation of cerebral parts may change these functional connections. This is the case in developmental disconnections (as an example presumed in the dyslexia complex (legasthenia) with reading-understanding-writing-hearing.[44,46] «Unused» areas may also exist as the result of an interruption of a connection-chain by disease.

Connections may return to another status in case of functional rehabilitation. Such brain areas hitherto «unused» may become reconnected from differing directions.[47,48]

Avinoam Safran and his PhD students,[27] using resting-state brain activity functional MRI in blinding ocular conditions, found that the primary visual cortex (V1) thoroughly reorganizes its functional connections to other areas of the brain. Thus, the part of V1 which has lost its visual input (e. g. foveal projection area in patients with Stargardt disease) and the remaining, still afferented parts, differently modify their connections, to either higher-order cognitive functions and top-down mechanisms, or to elementary other sensory cerebral structures.

To compensate for visual loss, residually-afferented V1 parts apparently strengthen connections to improve deficient functions, whereas sensory-deafferented V1 parts to tune-up higher-order mechanisms to assist perceptual processes.[27]

In another study, they reported[26] surprising changes in connectivity between visual cortex and language area, in individuals with retinitis pigmentosa. This was a first demonstration between the visual and language systems developing in adults, i. e. long after the end of a developmental sensitive period.[26]

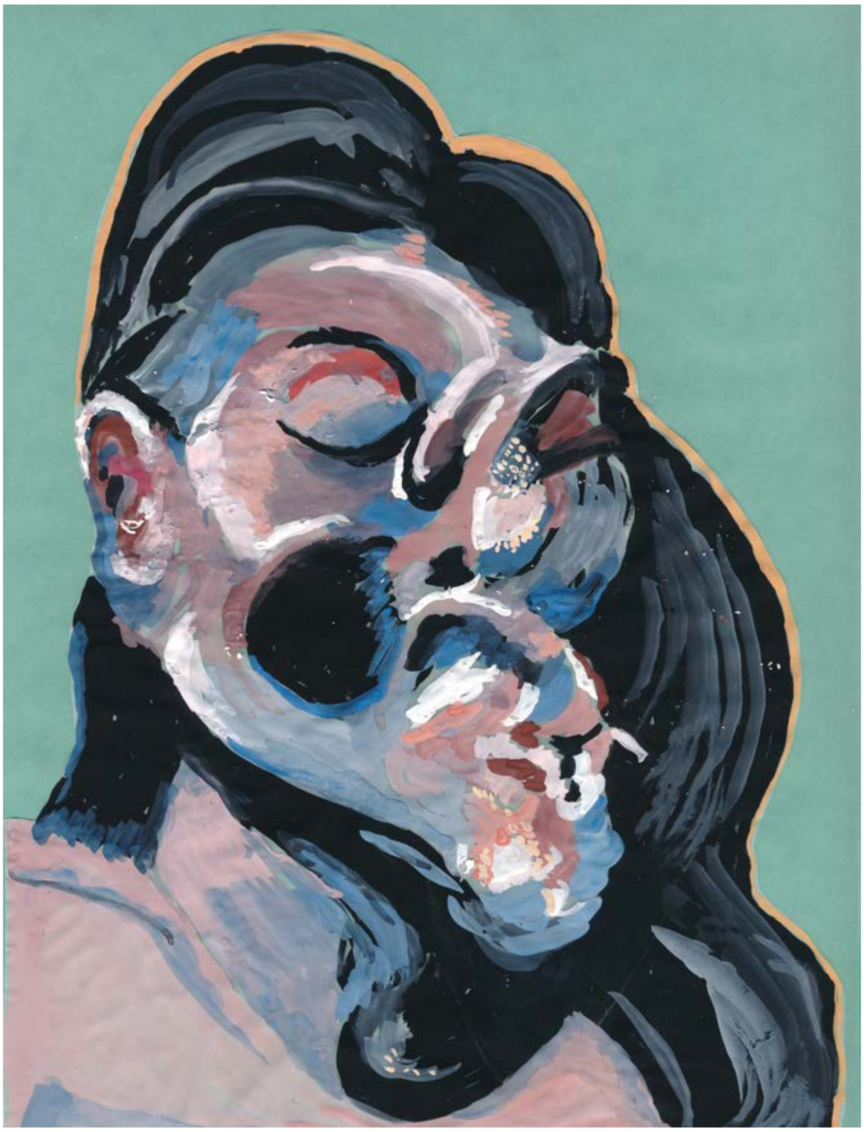

Fig. 4 Painting by Hannes Wildberger, inspired by the portrait of Henrietta Moraes, originally painted in 1963 by Francis Bacon (1909 – 1992).

Avinoam Safran: The power of aesthetics, … and more. The power of aesthetics in neuroscience.

Avinoam is a permanent observer, a scanner and collector of fascinating details over and beyond the edge of the ophthalmological dish. Ophthalmology alone is not enough. Something more, an aesthetic spice, some spirituality and the context with basic science of neighbouring disciplines enforce his points-de-vue. ➜

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