Lennart Gustafsson August 18, 2004

Two lectures on autism

This first lecture contains some of the material that has been published in

1. Gustafsson L. "Inadequate cortical feature maps: a neural circuit theory of autism" *Journal of biological Psychiatry* 1997; 42: 1138-1147.

2. Gustafsson L. "Neural network theory and recent neuroanatomical findings indicate that inadequate nitric oxide synthase will cause autism" In: Pallade V, Howlett RJ, Jain L, editors. Lecture notes in artificial *intelligence* 2003; Vol 2774, part II. New York: Springer-Verlag. P 1109-14.

3. Gustafsson L. "Comment on 'Disruption in the Inhibitory Architecture of he Cell Minicolumn: Implications for Autism'" The Neuroscientist 2004; Vol 10, Nr. 3, p. 189-191.

The second lecture will be based on the joint research by Lennart Gustafsson and Andrew Paplinski.

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Trying to understand autism through neural networks

Autism, or autism spectrum disorders, are enigmatic (gåtfulla).

Insights through mathematical analysis and computer simulations - is it possible?

The idea is gaining momentum.

I, for one, believe it's possible.

A broad picture
complete with a hypothetical explanation

It certainly is incomplete

It might even be wrong towards the end
(that's the nature of hypotheses)

but it surely fascinates me.

Autism

Leo Kanner (1943) in *Autistic Disturbances of Affective Contact*

Hans Asperger (1944) in *Die "Autistischen Psychopaten" im Kindesalter*

Ewa Scucharewa (1926) *in Die Schizoiden Psychopatien im Kindesalter*

Autism - what is it?

Diagnostic criteria, DSM-IV:

impairments in social interaction

impairments in verbal and nonverbal communication

restricted repertoire of activities and interests

Diagnostic criteria are based on behavior!

But – how is autism caused?

Up till the early seventies, psychodynamic (blame the mothers) explanations.

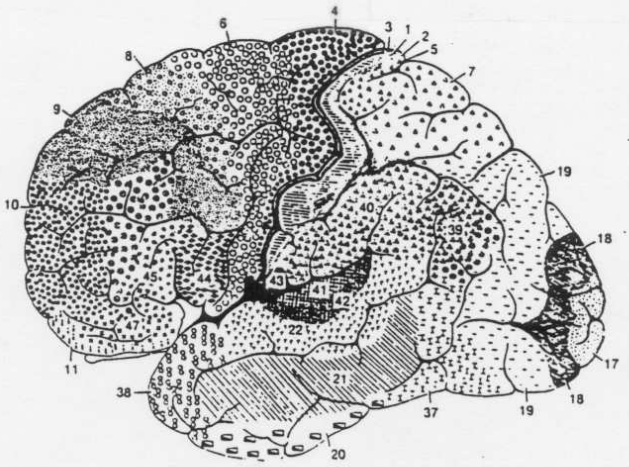
Presently biological explanations.

A multitude of brain abnormalities found in post mortem examinations and fMRI studies.

Few consistent findings (different individuals – different abnormalities).

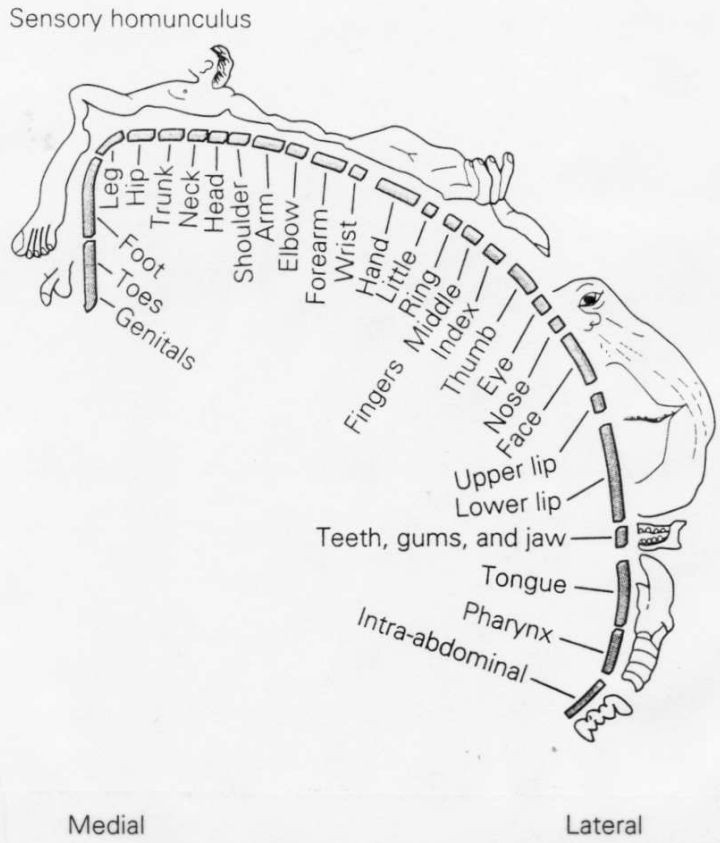
How do we start modelling?

A brain atlas by Brodmann from 1909

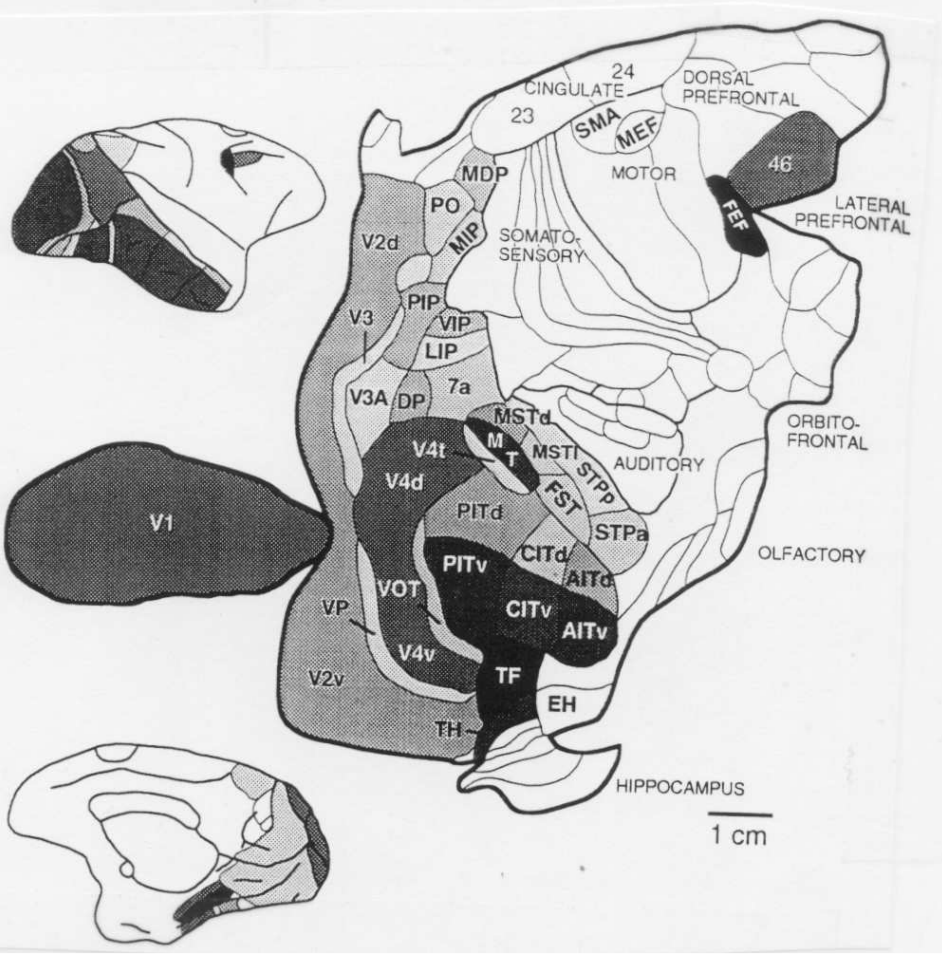


The different Brodmann areas fulfill different processing tasks- they are specialists – and they cooperate. The brain is a parallel processor.

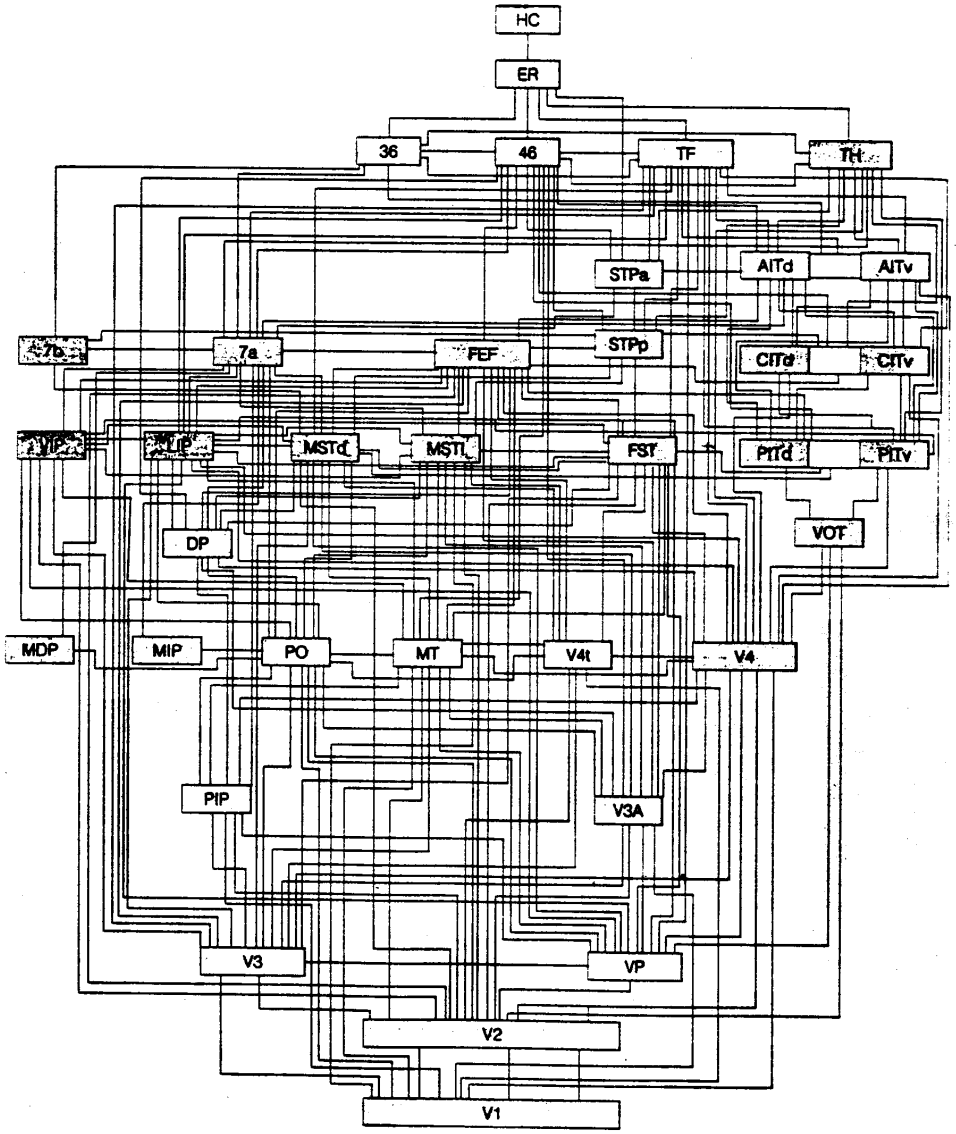
The primary sensory cortices correspond directly to the brain's environment, …



… whereas higher order sensory cortices make abstract representations of the world



This is not the final organization scheme from the HELA project, but the organization scheme of the macaque monkey vision



Whatever the level in the processing hierarchy, and the particular task there is a çommon architecture: the neural columns (mini- and macrocolumns).

Mountcastle 1957 …

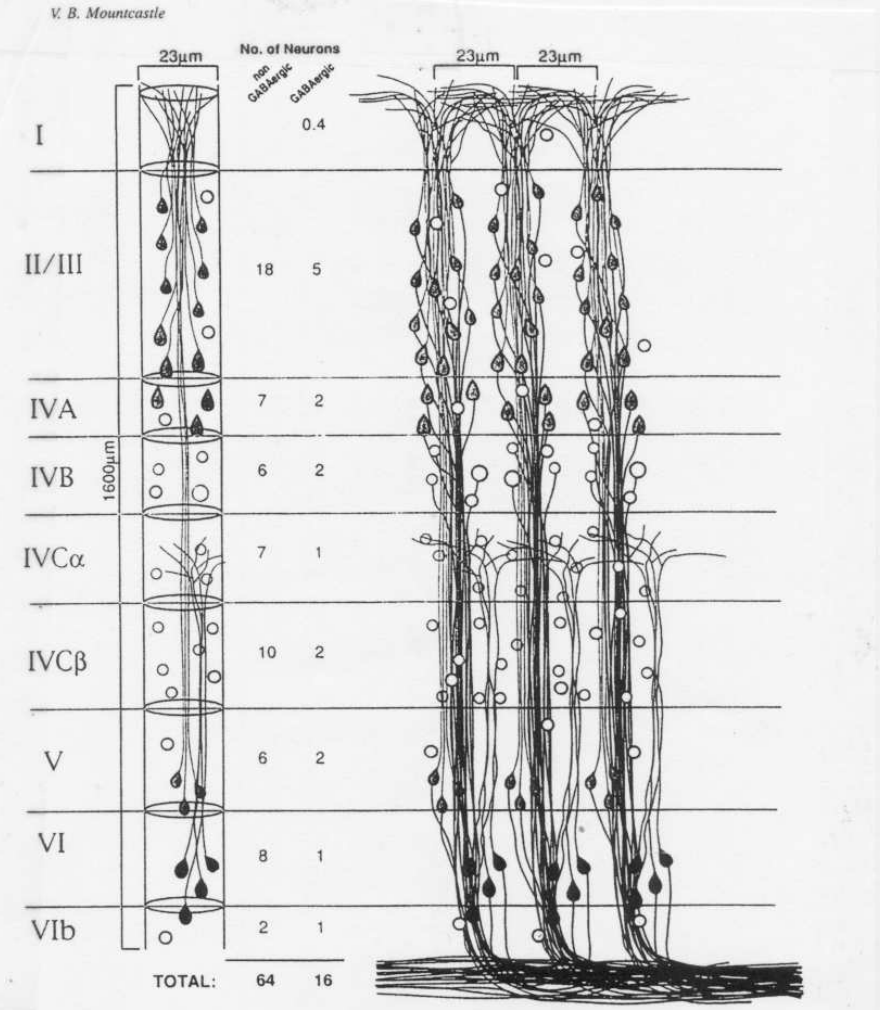


Fig. 16 Diagram of the arrangement of neurons, dendrites and axons in vertical modules of the striate cortex of the macaque monkey. *Left*. A drawing to show the arrangement of the apical dendrites of pyramidal cells; for clarity, only one-half of the neurons present are shown. The pyramidal cells in layers II/III, IVA and V are shown in red, those in layer VI in green. Neurons of IVB and IVC are shown without dendrites, in grey; GABAergic neurons in azure. Total numbers of GABAergic and non-GABAergic cells are given to the right of the drawing. *Right*. A drawing to represent the pyramidal cell modules (columns) showing the arrangement of dendrites and axons. Colour scheme the same as for the left, pyramidal cell axons are shown in blue. (From Peters and Sethares, 1996, with permission from Wiley-Liss.)

Artificial Neural Networks (ANN's) are

information extracting (from signals, stimuli) artefacts

learning artefacts – an ANN develops through learning, from building experience

designed with some influence from knowledge about the brain

The field was initiated by neuropsychologists for the study of mind/brain more than 50 years ago.

An Artificial Neural Network (ANN) is defined by

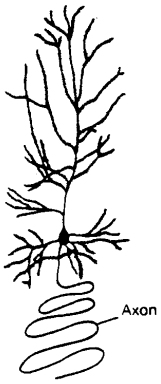
a model of a neuron

a network architecture

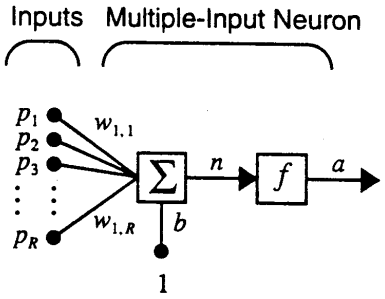
a learning rule

A sketch of a biological neuron

Pyramidal cell in cortex
(from Kolb & Whishaw)



A model (MATLAB) symbol for a neuron:



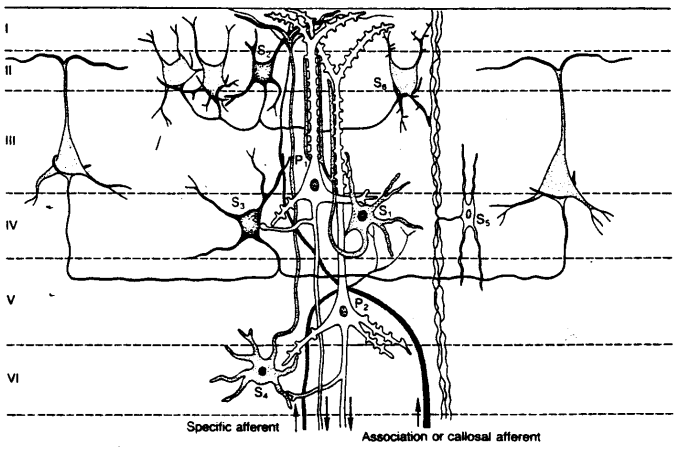
A mathematical model of a neuron:

$n = \Sigma w_i\, p_i + b$ $\quad$ w_i is the synapse "strength"

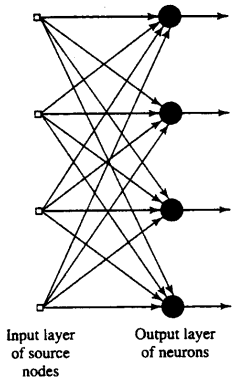
$a = f(n)$

Is the model simplifed? Certainly!

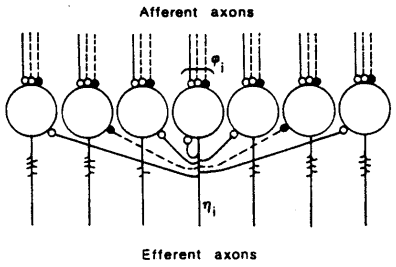
Biological network architecture
(from Kolb & Whishaw)



Artificial neural network (ANN) architectures



Feedforward network
(from Haykin)



Self-organizing network
(from Kohonen)

Are the ANN architectures simplified? Certainly!

Learning in an ANN:

Learning paradigms:

- Supervised learning
- Self-organization (unsupervised learning)
- (Reinforcement learning)

Hebb's law, 1949 – "neurons that fire together wire together" – experimentally established much later

"Technical improvements":

- Error back-propagation
- Winner Take All
- ...

How important is adherence to biological modelling of learning?

Theories of autism derived from theory of Artificial Neural Networks (I)

I.L. Cohen "An artificial neural network analogue of learning in autism" *Journal of Biological Psychiatry* 1994; 36:5-20.

Idea: too many neurons will cause autistic features, notably poor generalization.

Support: abnormally many neurons have been documented in parts of cortex in individuals with autism.

From Huttenlocker (1990):

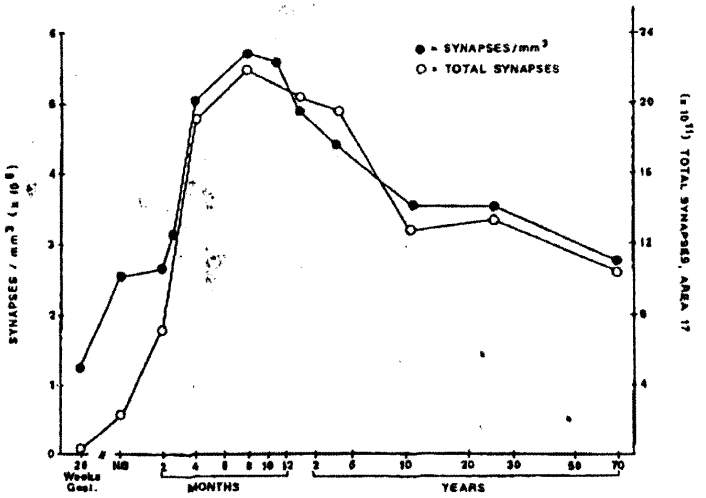
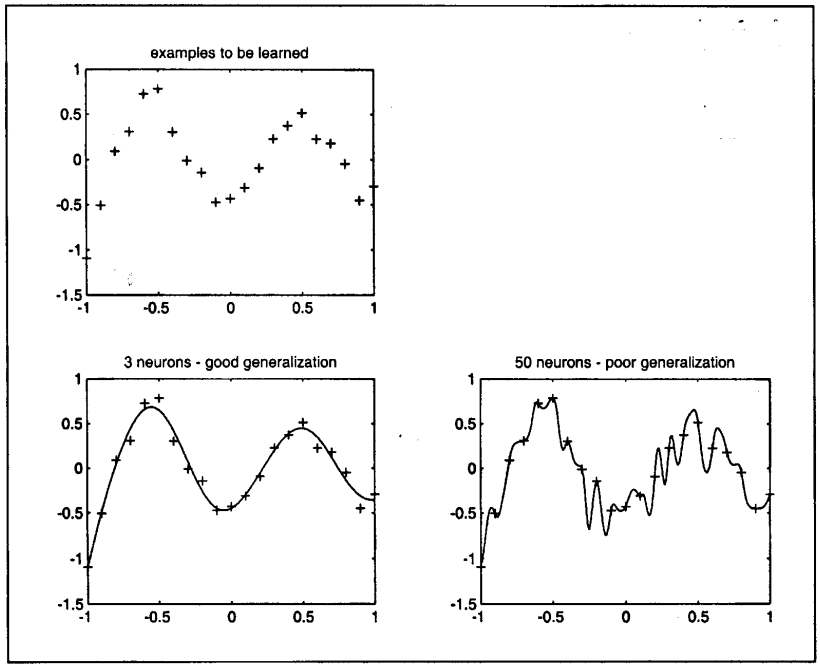


FIGURE 4.1. Synaptic density and estimate of total synapses in human visual cortex as a function of age. From Huttenlocher (1990). Copyright 1990 by Pergamon Press, Ltd. Reprinted by permission.

Why would too many neurons cause problems?



Neural networks with too many neurons for a given task will cause the network to learn exactly but be unable to generalize, i.e. produce reasonable outputs to inputs not learned.

Theories of autism derived from theory of Artificial Neural Networks (II)

L. Gustafsson "Inadequate cortical feature maps: a neural circuit theory of autism" *Journal of Biological Psychiatry* 1997; 42: 1138-1147.

Idea: cortical feature maps inadequately organized to process stimuli (signals) to extract information.

Signal activity drives self-organization of maps, consisting of neural columns as feature detectors.

With too narrow (and too many) neural columns cortical maps are not adequately organized to process stimuli or signals.

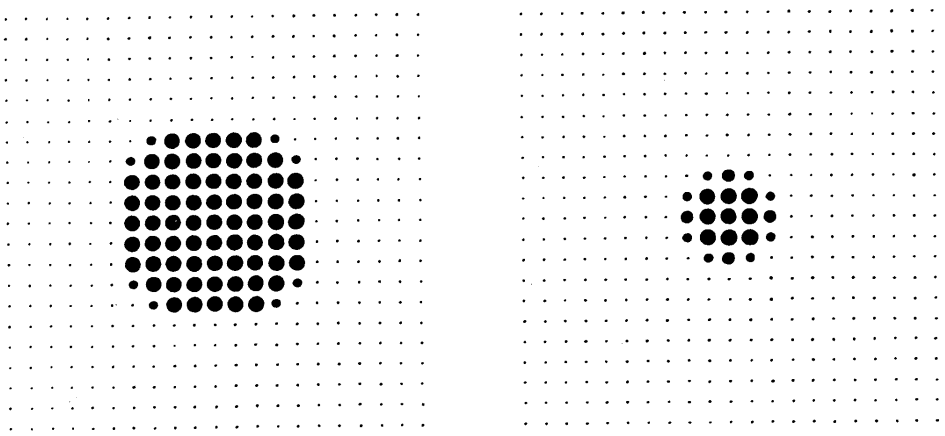
Verification

Manuel Casanova et al. (2002): "Minicolumnar pathology in autism"

Abnormal columnar organization (narrow and many minicolumns) in autism reported.

Hypothesis in my 1997 paper:

The inhibitory lateral feedback connections in cortex are excessive (in neural networks this causes narrow columns).

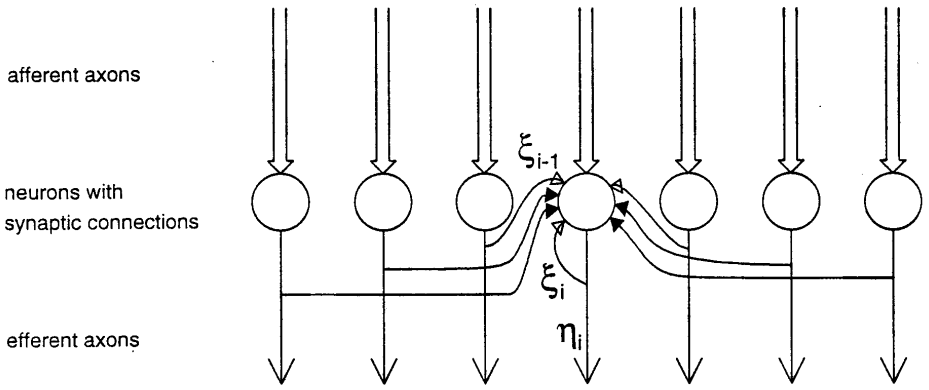


(a) (b)

Fig. 5.5a, b. Clustering of activity in a two-dimensional array. **(a)** Positive **(b)** Negative feedback stronger

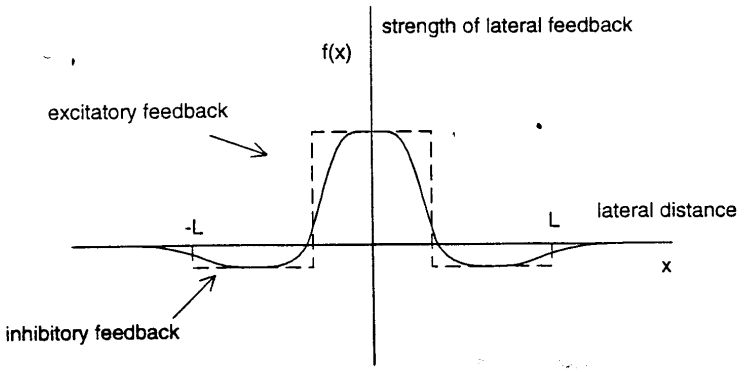
The next step: explain how narrow neural columns emerge

Neural columns emerge in neural networks when there is a proper balance between lateral excitatory and inhibitory feedback connections.



excitatory lateral feedback

inhibitory lateral feedback



Difficulties with my 1997 hypothesis:

Epilepsy is a common comorbidity with autism, these cases are helped by increasing one kind of synaptial inhibition.

Which inhibitory neurotransmitter/modulator would be a possible candidate – where is the smoking gun?

Alternate/complementary explanations

A serotonin abnormality

A nitric oxide abnormality

A serotonin abnormality

The most consistent finding in searches for a genetic linkage to autism.

One report (Chugani et al.) shows that children with autism have an initially low production capacity of serotonin in the CNS but maintains that capacity.

Serotonin plays a role in synaptogenesis (at least in rats).

A high level of serotonin causes barrel fields in rats to almost merge a low level causes narrow barrel fields.

An alternate hypothesis - background

Cortical self-organization with neural columns may emerge without lateral feedback, only relying on the mechanism of a diffusible messenger – nitric oxide, NO.

Gally, Montague et al. supported this hypothesis through neural network simulations in the beginning of the nineties.

Bart Krekelberg and John Taylor supported this hypothesis through mathematical analysis in 1996-97.

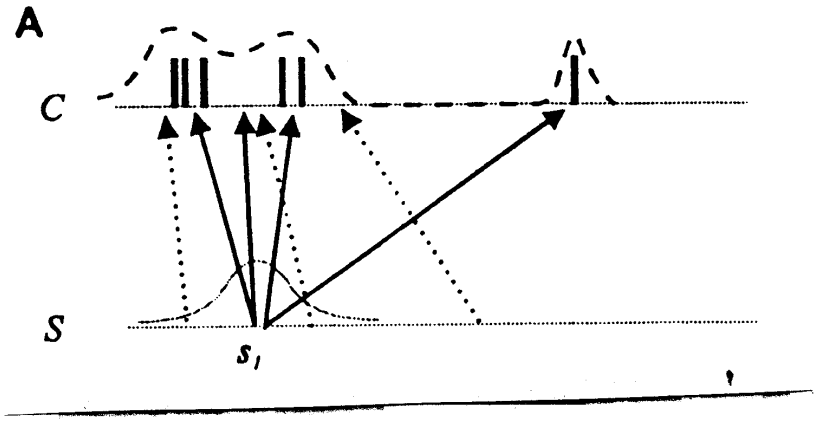
Their analysis showed that low production of NO causes narrow neural columns.

(Would any psychiatrist read Krekelberg and Taylor?)

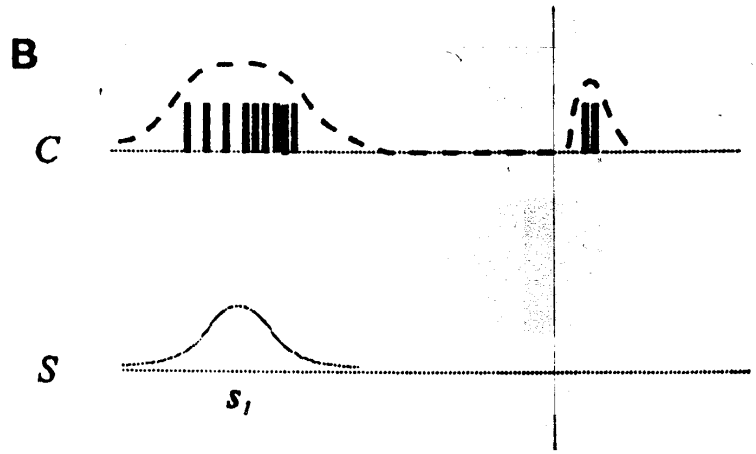
How does it work?

From Krekelberg and Taylor:

Excitation from sensory surface S causes somewhat scattered activity in cortex C. NO is released at activities and spread.

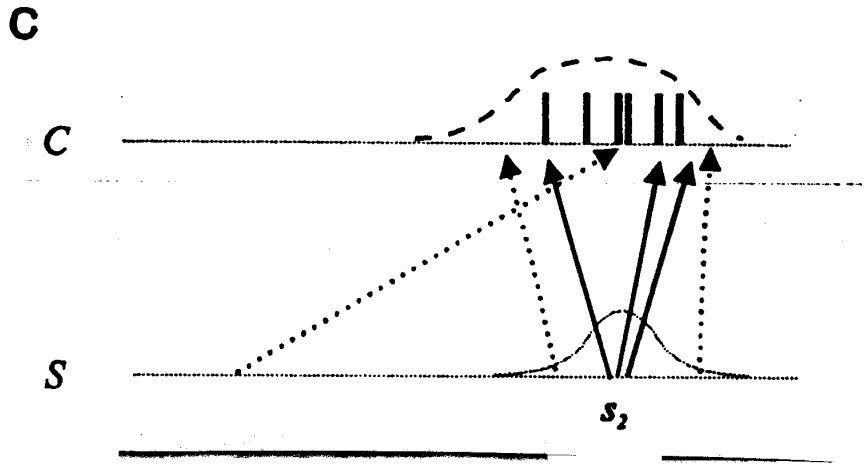


The same excitation from S causes more compact activation in C but some extraneous activation is also present.

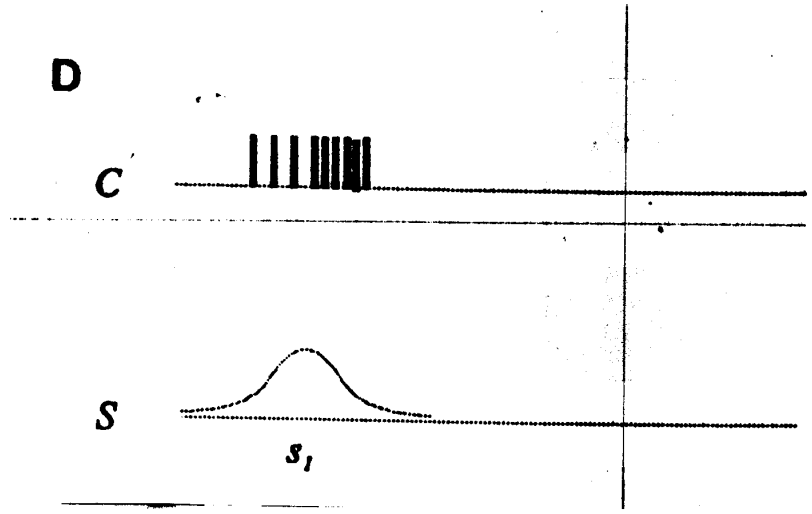


How does it work? (Cont.)

A different excitation in S weakens the connection that caused the previous extraneous activation.



The first excitation now causes only one compact bubble of activity, a neural column in one dimension.



Rules for changing synaptic strengths
(from Gally & Montague)

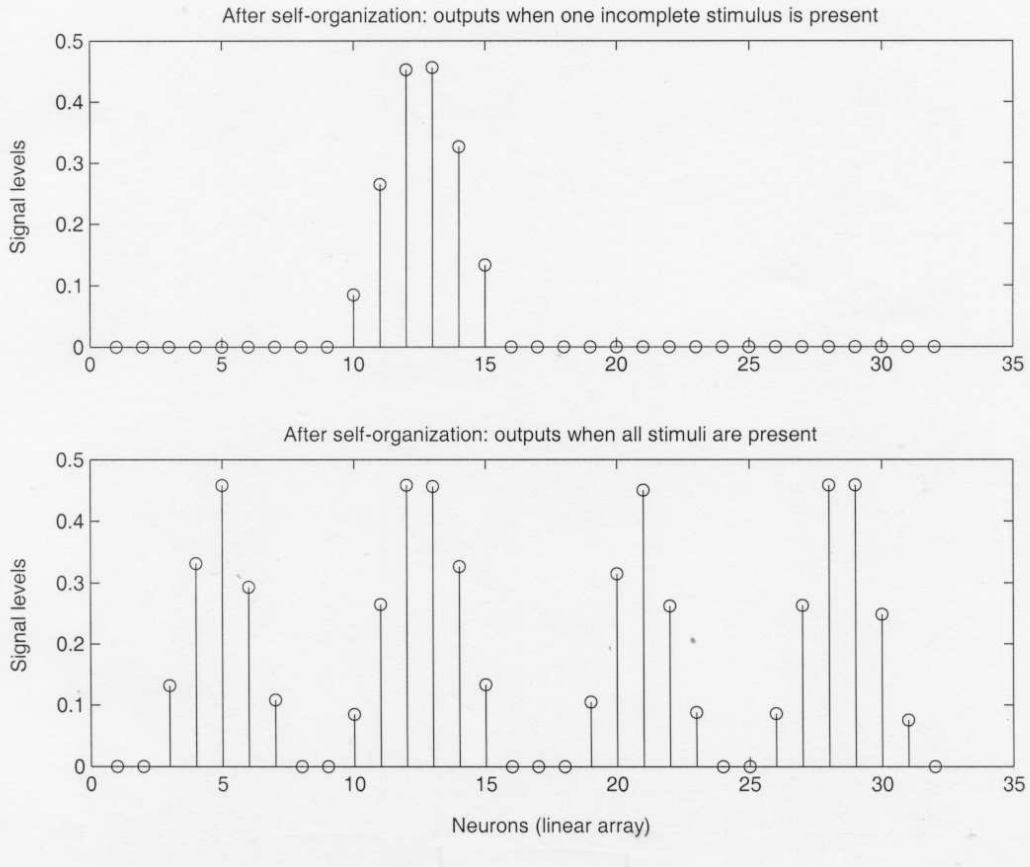
Table 1
Rules for changes in synaptic strength

	High [x]	Low [x]
Presynaptic terminal firing	increase	decrease
Presynaptic terminal not firing	decrease	no change

[x], concentration of diffusible signal. High [x] and low [x] represent values of [x] that are above or below thresholds for potentiation or depression. See Appendix 1 for these thresholds.

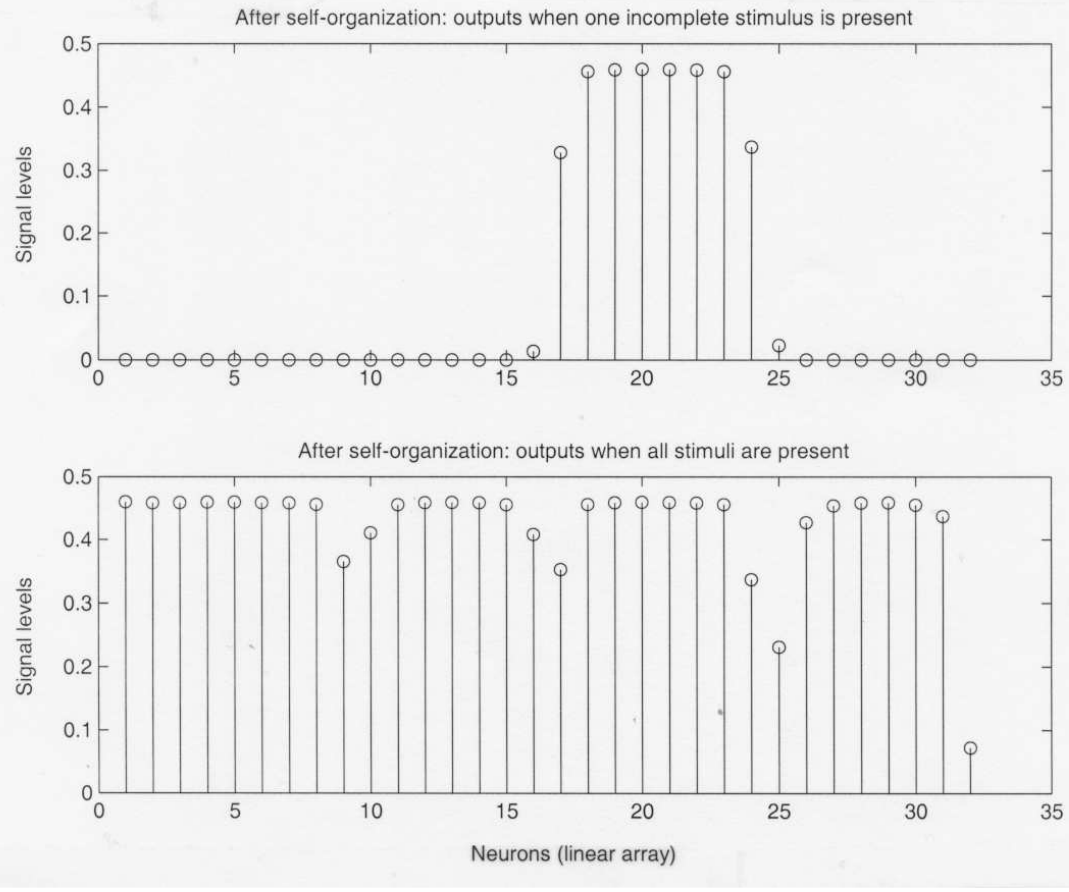
A simple simulation

Adequate NO – discriminating neural columns with high outputs.



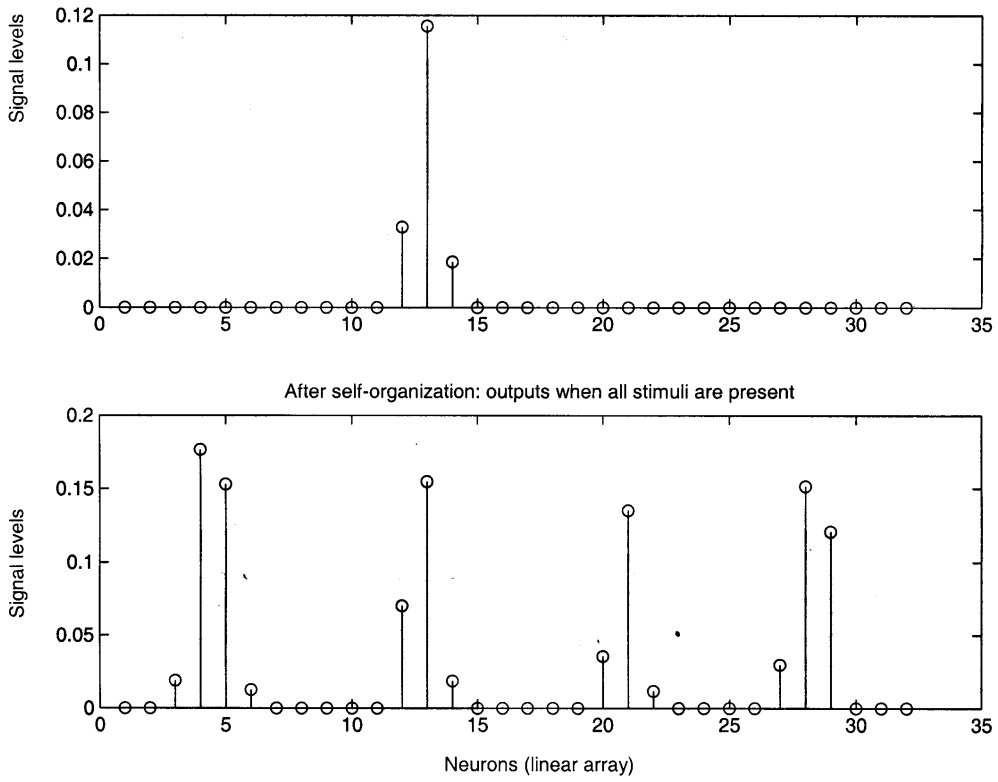
A simple simulation

Too much NO – neural columns don't discriminate well.



A simple simulation

Inadequate NO – neural columns narrow with low outputs.



Two-dimensional neural columns, entirely driven by nitric oxide

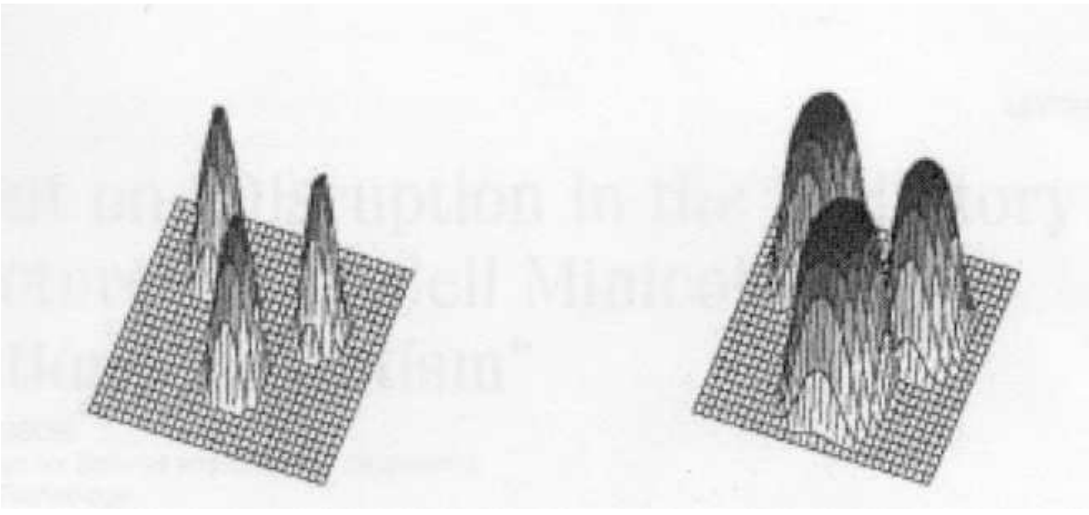


Fig. 2. Narrow and wide neural columns driven by the nitric oxide level.

In the left map the supply of nitric oxide was low, in the right map it was high.

An alternate hypothesis - presentation

Neural network theory and recent neuroanatomical findings indicate that inadequate nitric oxide synthase will cause autism

Presentation at session on "Neural network models of brain disease, plasticity and rehabilitation" at a conference in Oxford this September.

The neural network part has been covered – inadequate NO will cause narrow neural columns.

What about the recent neuroanatomical findings?

Neuroanatomical finding I:

Abnormal early brain growth in autism

Many papers in recent years (Eric Courchesne and others) report this.

Another question of balance!

Neurotrophins causes the brain to grow.

"Arresting factors" balances this growth.

NO is an arresting factor. Inadequate NO will result in abnormal brain growth.

Neuroanatomical finding I (cont.):

The abnormal brain growth is not uniform. The occipital lobe (visual cortex) is not much affected.

Vision is relatively spared in autism.

Csillik et al. (1998, animal experiments): NO is not important in columnar organization of area 17 in the occipital lobe (primary vision area) but for the prefrontal lobe (heavily affected in autism).

Tobin et al. (1995, animal experiments): Inhibition of NO does not impair visual discrimination.

Neuroanatomical finding II:

A deficit of Purkinje cells in the cerebellum

This is one of the few consistent finding in autism

Hypothesis by Courchesne in 2002: abnormal growth of the cerebrum causes excitotoxicity which kills Purkinje cells.

Snyder (1993): NO can play a neuroprotective role.

Chiani t al. (2001): NO can protect against some forms of excitotoxicity.

It is possible that a lack of NO could diminish the chances for Purkinje cells to survive.

Granule cells of the cerebellum?

Animal experiments lend further support to the hypothesis that inadequate NO will cause autism:

Motor problems

Sleep problems

Aggressive behavior

Nociception (pain) from thermal and mechanical abuse

The famous Janus face of nitric oxide

Nitric oxide is synthesized from nNOS, eNOS and iNOS.

The effects of nitric oxide often depends on the source and the effects from different sources are often antagonistic.

Nitric oxide from nNOS (and possibly iNOS) is proconvulsant

Nitric oxide from eNOS is anticonvulsant

Could there be subclasses of autism with characteristics as follows?

Insufficient eNOS will (in mice):

Make it easier to induce epilepsy
Make aggressive behavior in males less likely
Cause anxiety in certain learning situations

Insufficient nNOS will (in mice):

Make it more difficult to induce epilepsy
Make aggressive behavior in males more likely
Reduce sleep
Reduce pain from mechanical and thermal abuse

Two lectures on autism
Second lecture

This second lecture reflects our current level of understanding of the importance of the nature of the attention shifting abnormality that is prevalent in autism.

We have previously used two-dimensional stimuli and results obtained have been published in

Gustafsson L. and Paplinski A., "Self-organization of an artificial neural network subjected to attention shift impairments and novelty avoidance: Implications for the development of autism", *Journal of Autism and Developmental Disorders*, Vol. 34, No. 2, pp. 189-198, April 2004.

In this lecture we use higher-dimensional stimuli and draw from a conference presentation:

Paplinski A and Gustafsson L., "An attempt in modelling early intervention in autism using neural networks", in Proceedings 2004 IEEE International Joint Conference on Neural Networks, Vol.1, pp. 29-34.

Effects of self-organization under restricted attention shifting

There is an attention shifting abnormality in autism.

But is it caused by:

a general attention shifting impairment?

or

a restriction of attention shifting by familiarity preference?

There are proponents for both hypotheses.

A neural network test of the two hypotheses

Objects from two sources are randomly presented to a self-organizing neural network which will adapt to the objects, i.e. learn them.

Source A contains animals of a wide assortment

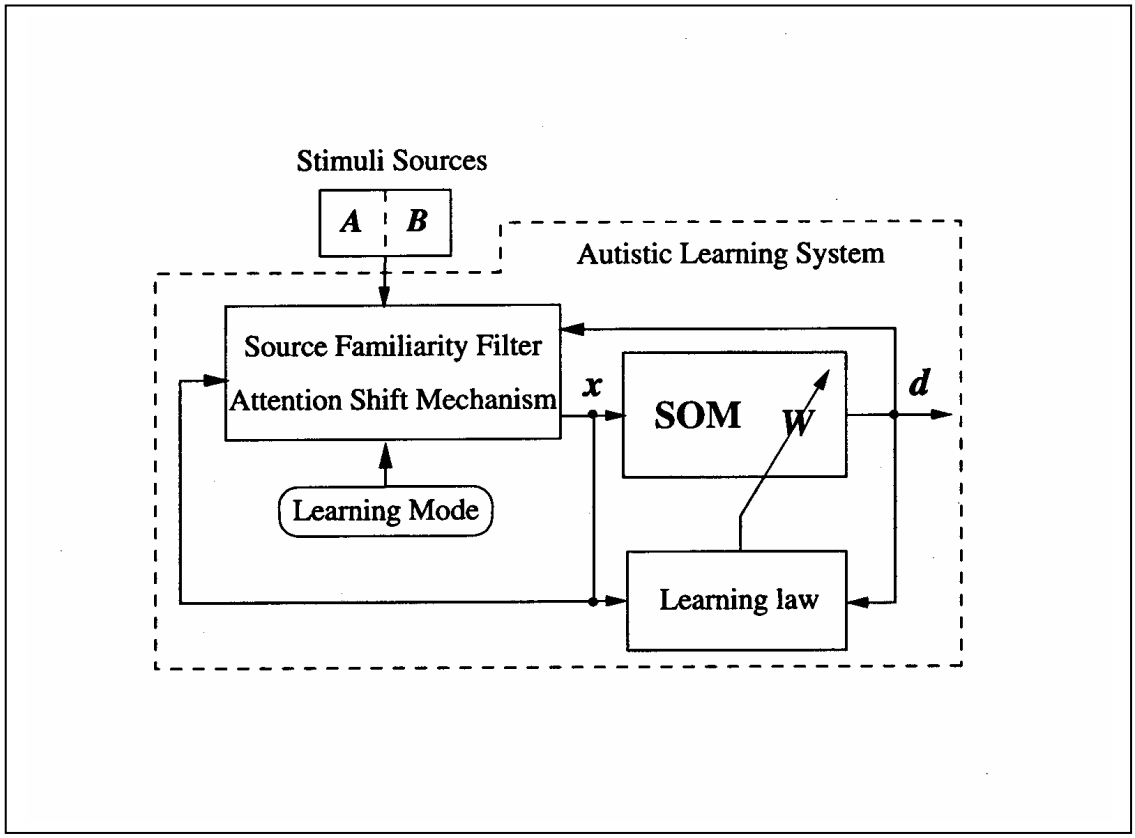
Source B contains different felines

Source B has objects with little variability compared to source A.

Which object will the network learn?

It depends on the character of the attention shifting.

A block diagram of learning for the purpose of testing the importance of different attention shifting mechanisms



Attention shifting modes

Mode 1: attention shifts to the source presenting a new object (novelty seeking learning)

Mode 2: attention shifts to the source presenting a new object but only with a low probability (general attention shifting impairment)

Mode 3: attention shifting

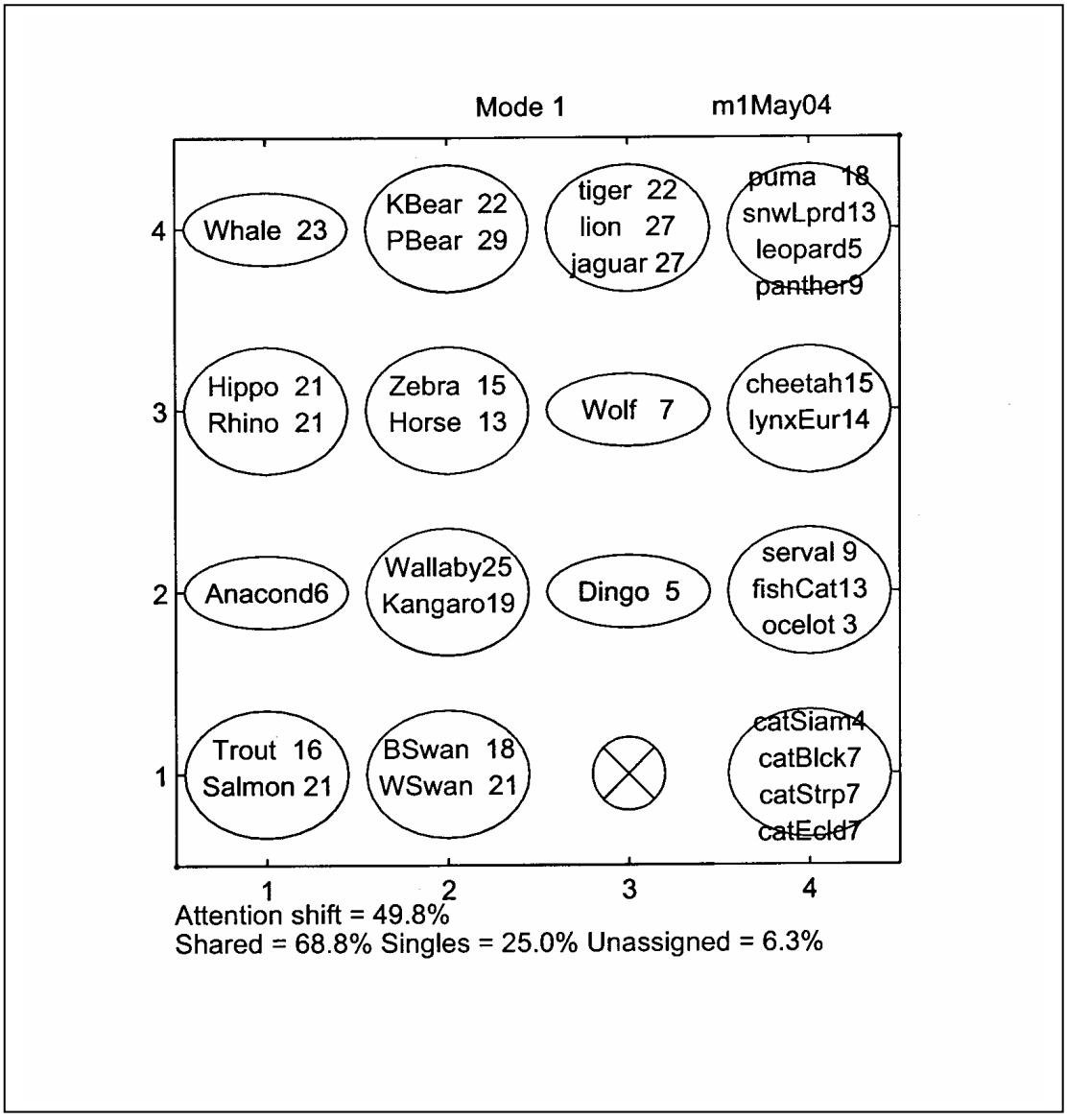
initially to the source presenting a new object

then with a preference for the most familiar source

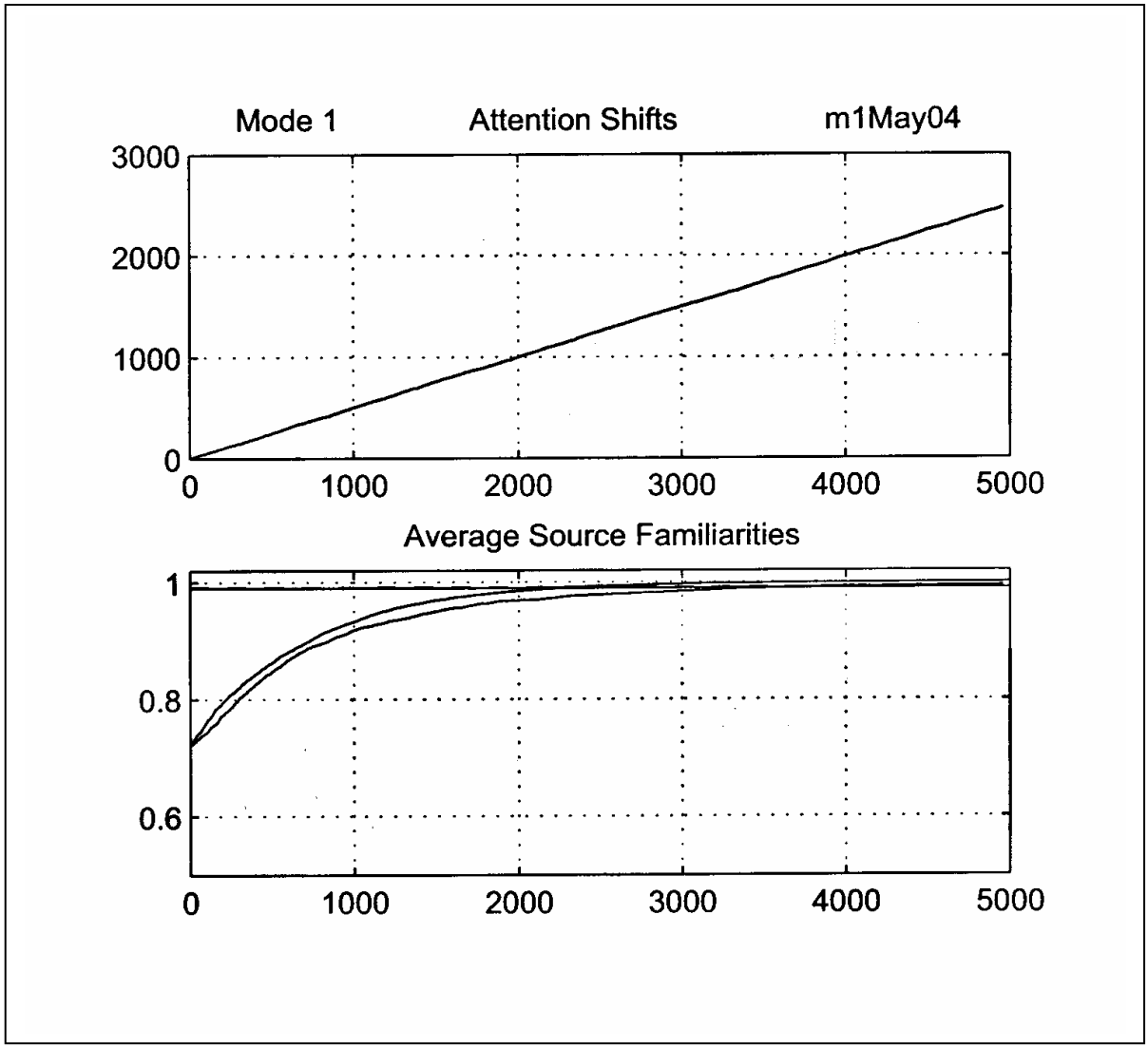
then last,

if both sources have become well familiar, to the source presenting a new object
if both sources have not become familiar attention shifting ceases.

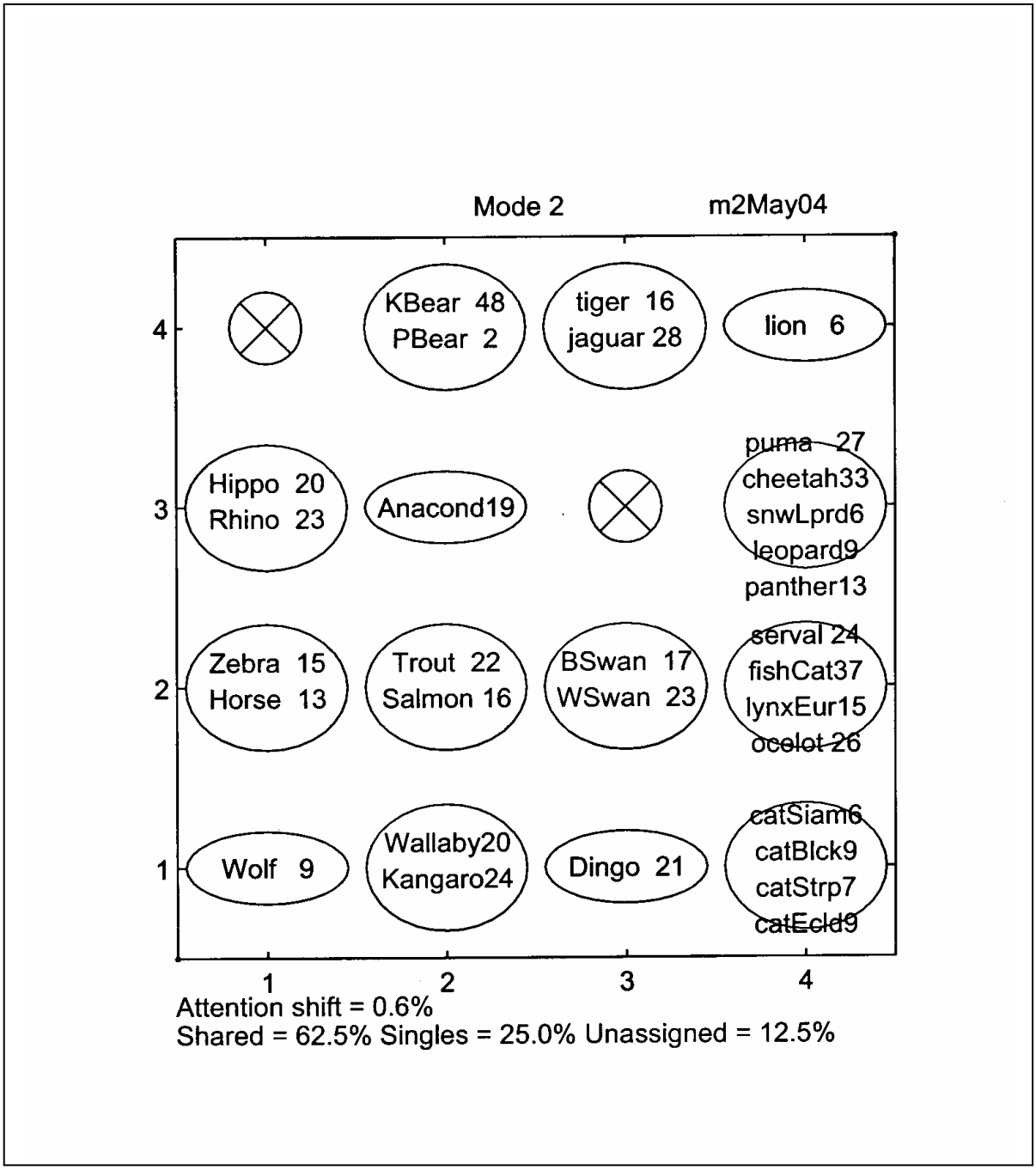
Resulting map from learning with normal attention shifting (attention shifted to source of new stimulus). Stimuli from both sources are learned well.



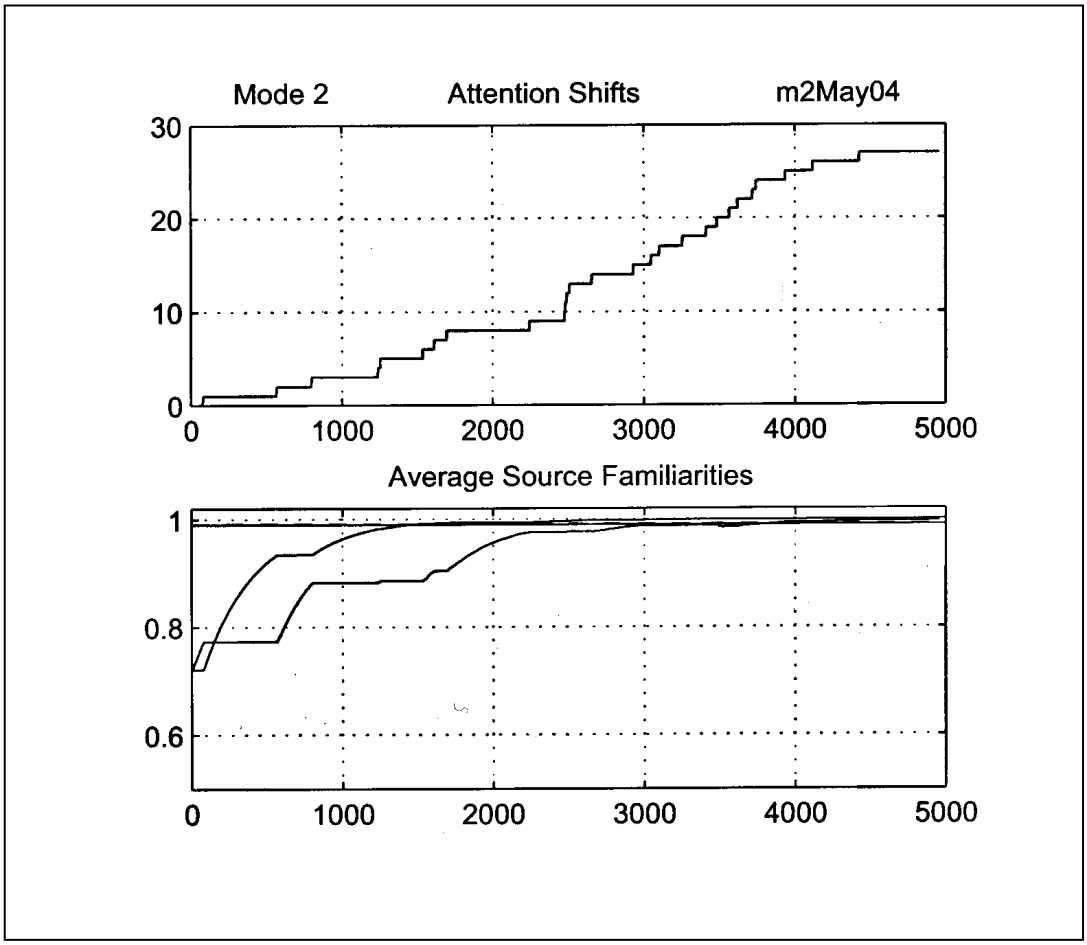
Number of attention shifts grows linearly in normal attention shifting. The familiarity with source B grows faster than familiarity with source A.



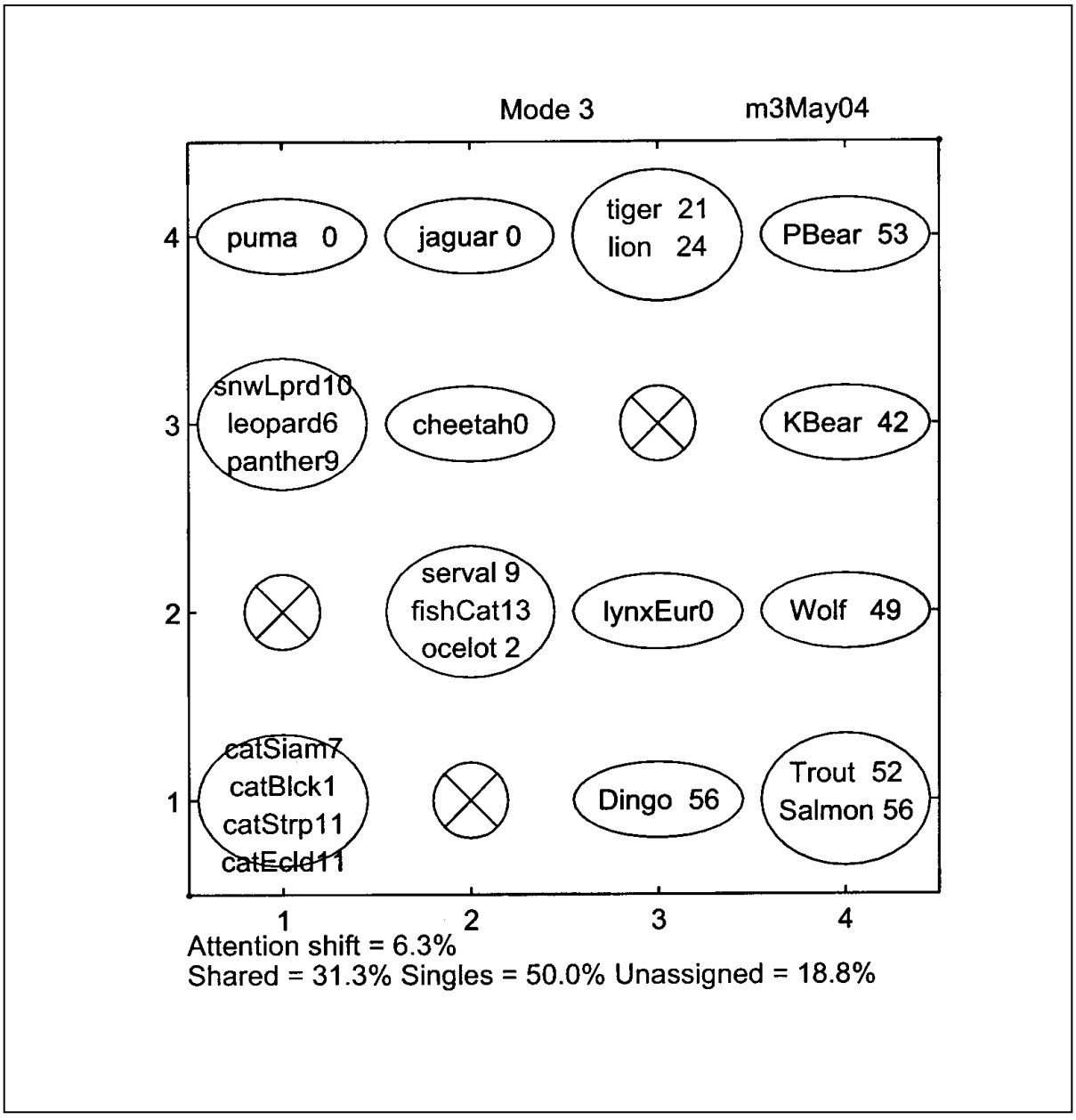
Resulting map from learning with a general attention shifting impairment (attention shifted to source of new stimulus with low probability). Stimuli from both sources are learned well.



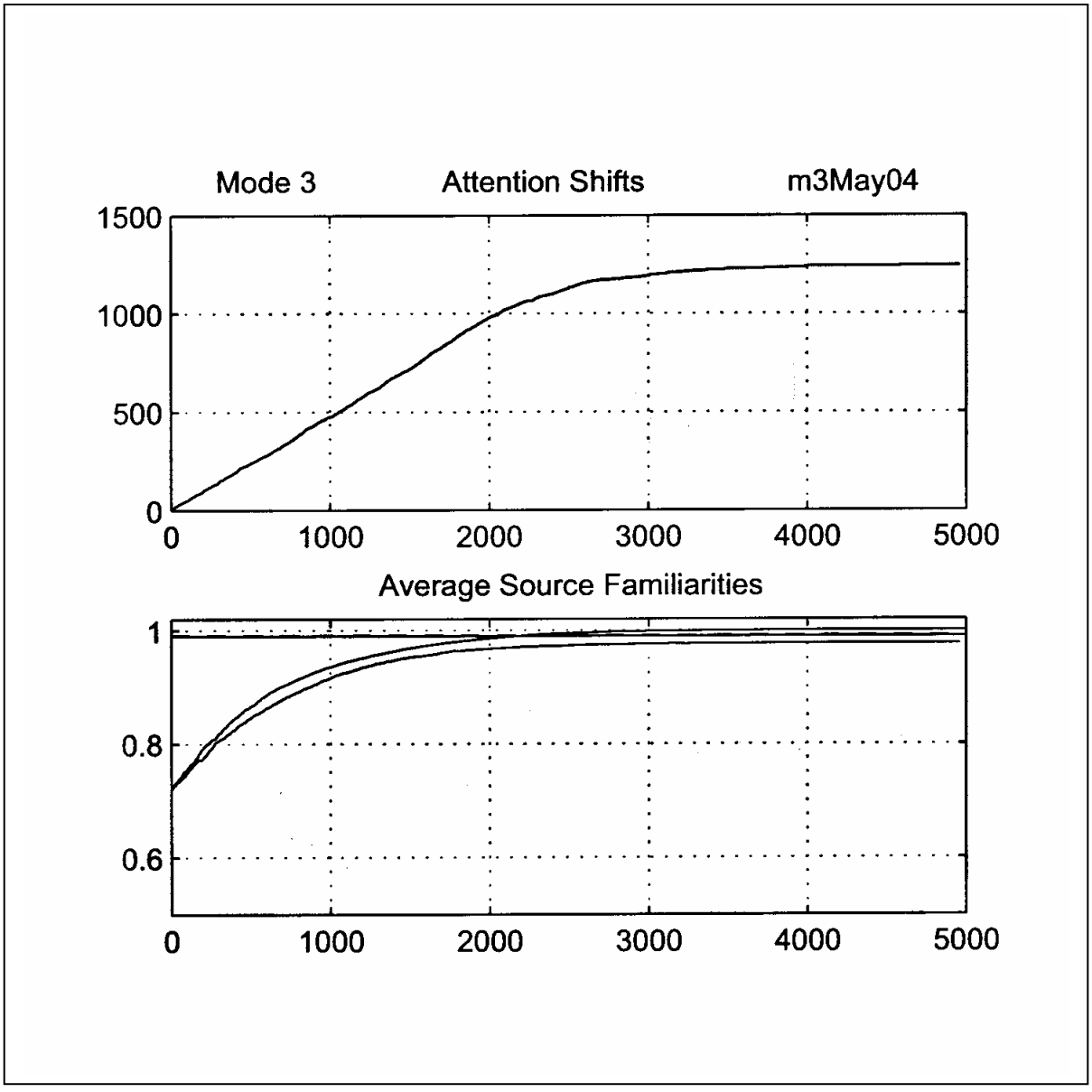
Number of attention shifts grows sluggishly in general impairment of attention shifting.



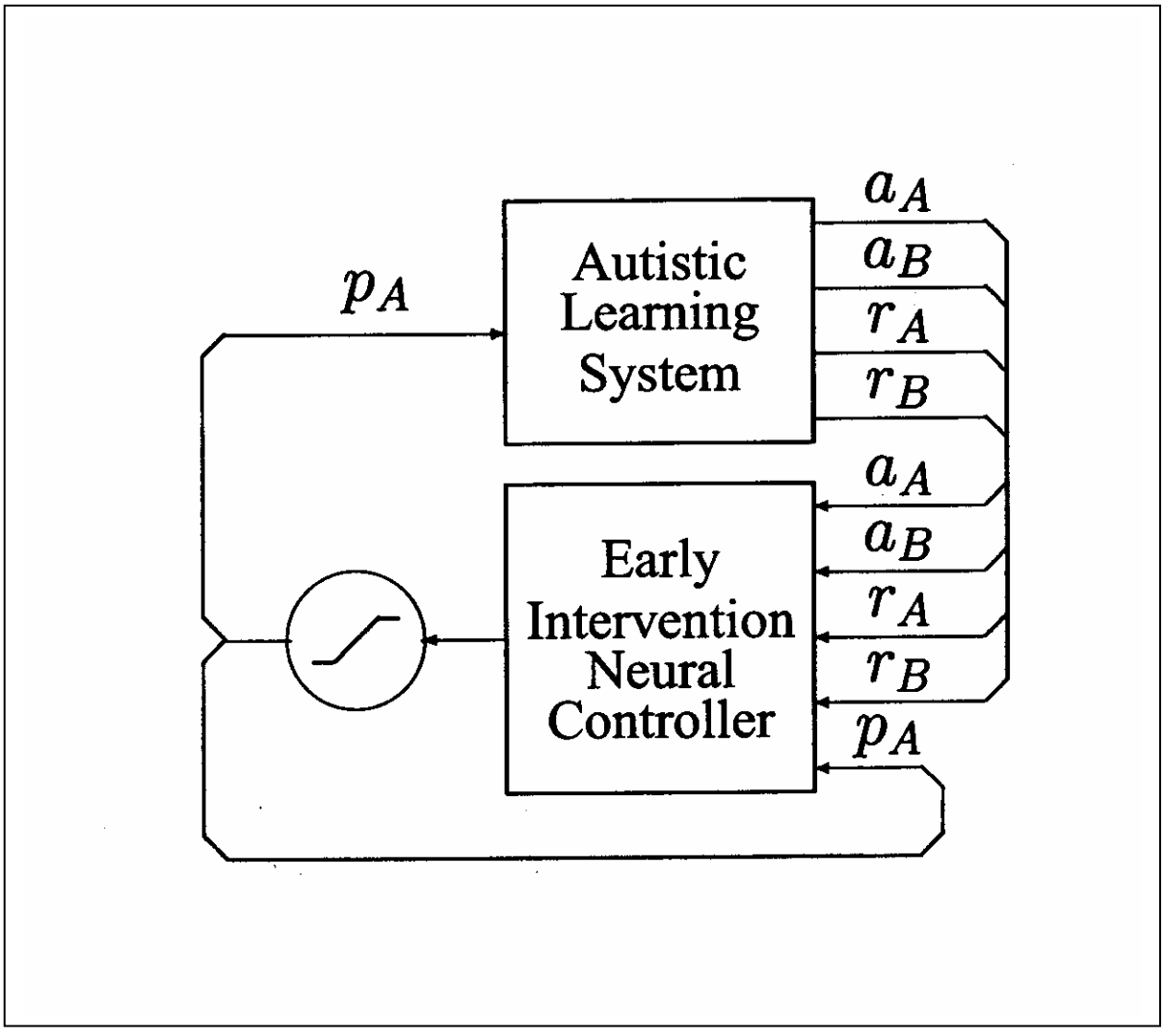
Resulting map from learning with attention shifting restricted by familiarity preference. Stimuli from source B (the source with the lowest variability are learned well.



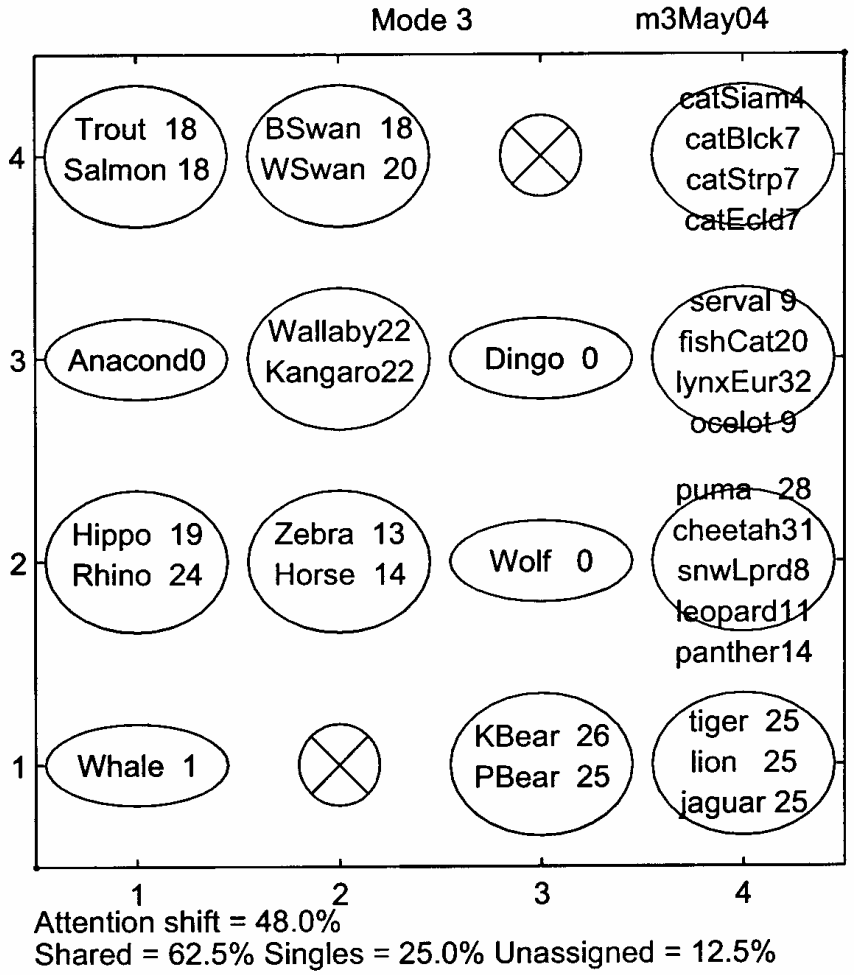
Attention shifting ceases to occur when source B has become familiar (above a threshold level) and is also more familiar than source A.



Observations of attention shifting are fed into an early intervetion controller to counteract the ceasing of attention shifting. Observations include acceptance of attention shifting to a source (and) and rejection of attention shifting to a source (and). The probability for the next stimulus coming from source A is the output of the controller. When a source is starting to be rejected it is given more chances for exposure to the self-organizing map.



Resulting map from learning with attention shifting restricted by familiarity preference *and* early intervention. Stimuli from both sources are learned well.



The controller steps in to give source A preferential treatment. There will be an overshoot so it will have to change the preferential treatment several times before the map will become familiar with both sources. Attention shifting to both sources resumes.