Table 1
Immune parameters affected by behavioral conditioning paradigms

Conditioned stimulus	Unconditioned stimulus		Conditioned response
Taste/odor	Immunosuppressant drugs	↓	Antibody production Lymphocyte proliferation Hypersensitivity Allergic response Allograft rejection NK-cell activity Cytokines
Taste/odor Auditory/visual Touch	Immunostimulating drugs/antigens	↑	Skin hypersensitivity NK-cell activity CTL activity Neutrophil activity Antibody production Histamine release Anaphylaxis Complement

Brain, Behavior, and Immunity 20 (2006) 430–446

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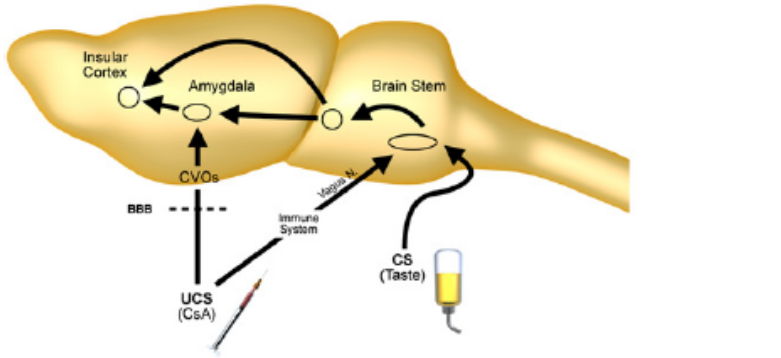


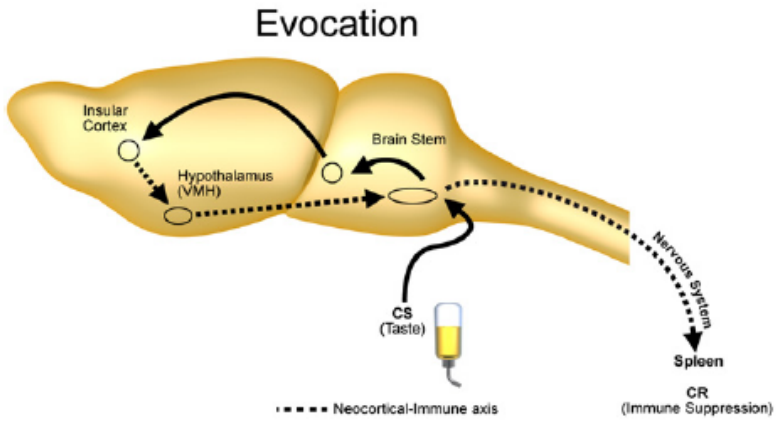
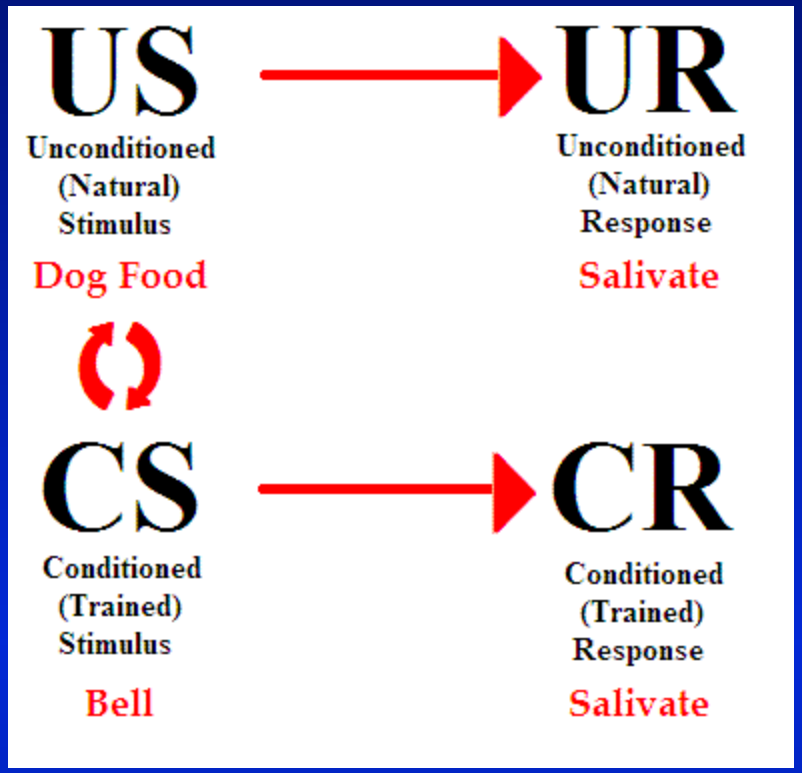


Figure 2. Neural Substrates Involved in Behaviorally Conditioned Immunosuppression in Rats

Brain excitotoxic lesions show that the insular cortex is essential to acquiring and evoking this conditioned immunosuppressive response. In contrast, the amygdala seems to mediate the input of visceral information necessary at acquisition time, whereas the ventromedial hypothalamic nucleus appears to participate in the output pathway to the immune system needed to evoke the behaviorally conditioned immune response (CS, conditioned stimulus, saccharin taste; UCS, unconditioned stimulus; CsA, cyclosporine A; BBB, blood-brain barrier; CVOs, circumventricular organs; VMH, ventromedial hypothalamic nucleus) (Pacheco-Lopez et al., 2005).

Geneesmiddel

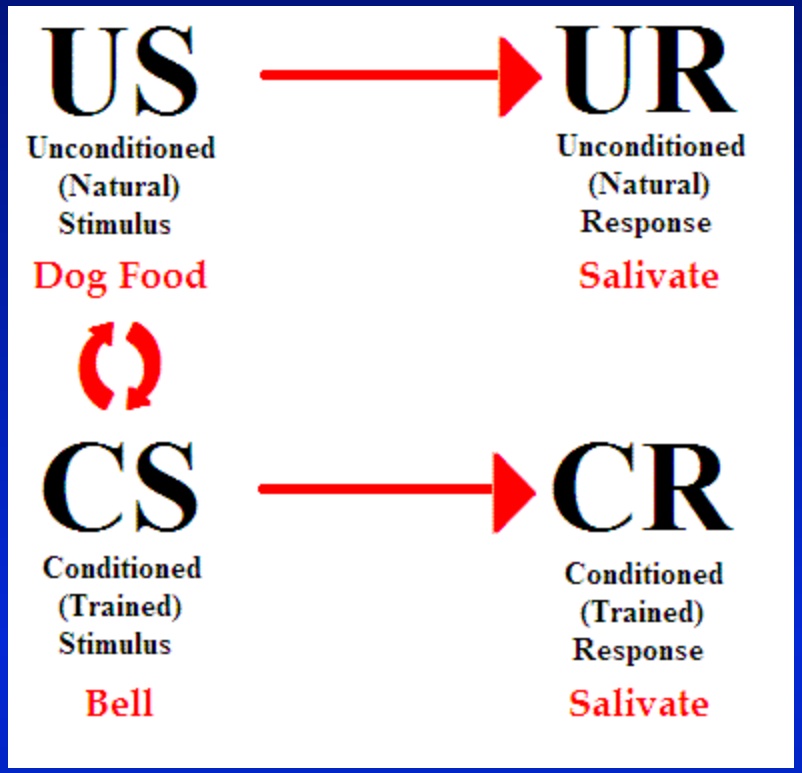


Opknappen

Opknappen

Geneesmiddelverpakking
Kamer (kleur/geur)
Behandelaar
Handeling (injectie, pil met glas water)
Etc…

Amfetamine injectie

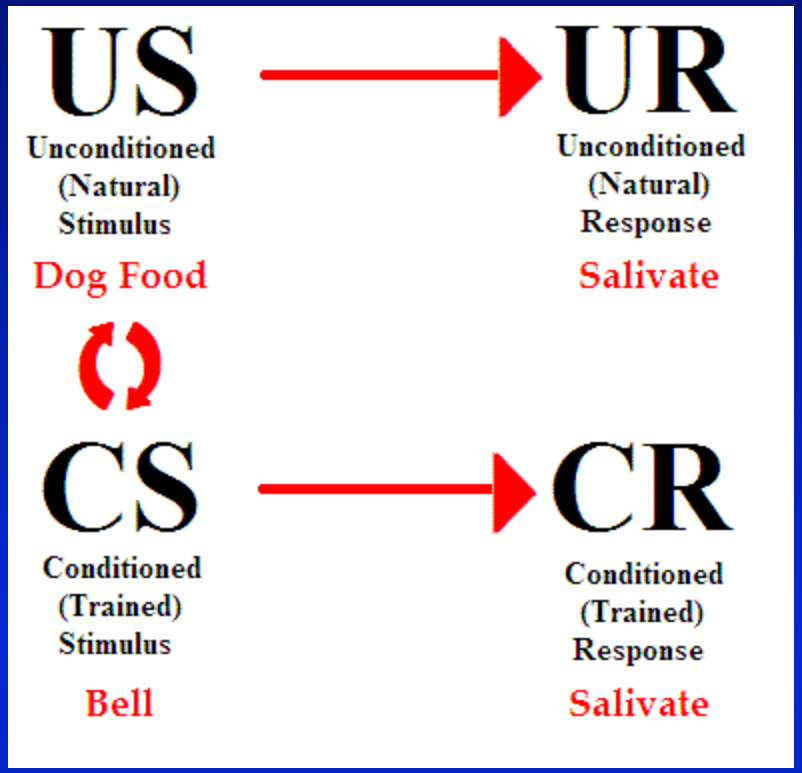


Hyperactief

Hyperactief

Fysiologisch zout Injectie,

Dexamethason

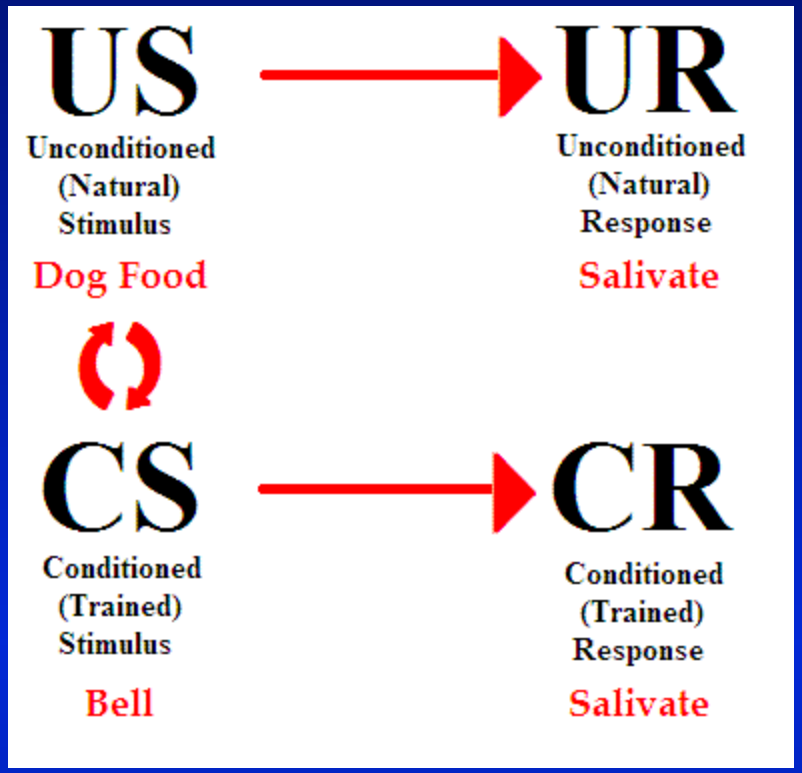


C’ costeroide effecten

Cortisolsecretie
En C’ costeroide effecten

Smaak

huismijt



allergie

allergie

inhaleren

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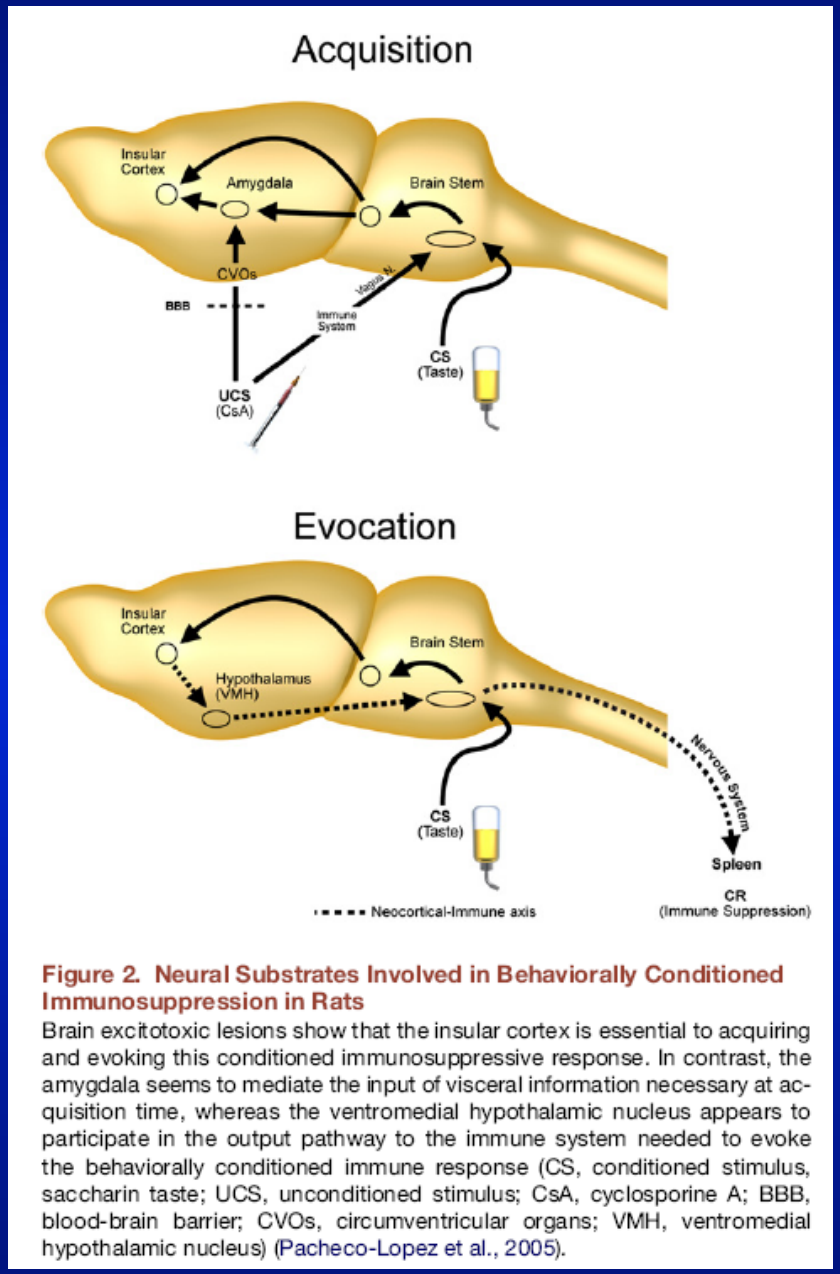

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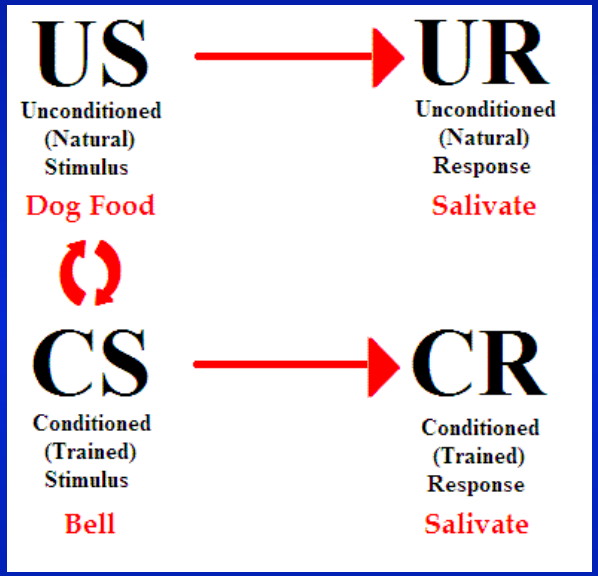
Ketorolac (NSAID)



Pijn red.

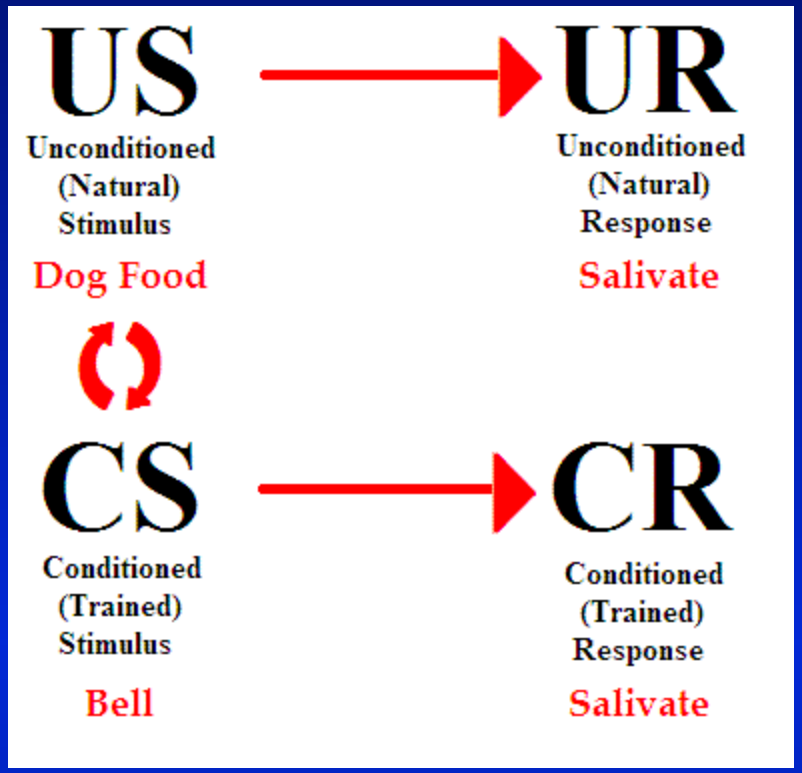
Injectie procedure

Pijn red.

Niet te remmen door naloxon

chemo

braken



reminder

braken

Table 2
Placebo effects in inflammatory and immune-related diseases

Disease	Placebo effects	Methodological issues	Reference
Asthma	Pooled placebo effect in stable asthmatics during long-term drug therapy trials was small but measurable. A modest number of patients receiving placebo (6%) showed changes in pulmonary function that can be considered clinically relevant.	33 randomized double-blind placebo-controlled clinical trials, 1243 patients.	Joyce et al. (2000)[a]
Cancer	Placebo treatment associated with slight improvement in symptoms such as pain (9%) and appetite (20%) but rarely with positive tumor response (2.4%). A significant part (10–60%) of nocebo effects is associated with "inert" treatments.	37 randomized placebo-controlled trials: Pain 12 trials, 405 patients; Appetite 5 trials, 368 patients; Tumor size 10 trials, 464 patients.	Chvetzoff and Tannock (2003)[b]
Crohn's disease	Mean placebo response rate was 19%. Number of office visits, duration of study and disease severity at entry influenced placebo response.	32 placebo-controlled trials, 1047 patients.	Su et al. (2004)[a]
Chronic fatigue syndrome	Pooled placebo response was 19.6%. Psychological-psychiatric interventions showed a low placebo response (14%), whereas infectious-immunological and alternative-complementary interventions showed a high placebo response (24%).	29 randomized placebo-controlled trials, 1016 patients.	Cho et al. (2005)[a]
Duodenal ulcer	Pooled healing rate in placebo groups ranged from 36.2 to 44.2%.	79 randomized placebo-controlled trials, 3325 patients.	de Craen et al. (1999a,b)[a]
Irritable bowel syndrome	Placebo response ranged from 16 to 71% with a population-weighted average of 40%. Study duration and the number of visits/study duration did not significantly influence the placebo response.	45 randomized placebo-controlled trials, 3193 patients.	Patel et al. (2005)[a]
Multiple sclerosis	Relapse frequency in remitting-relapsing MS patients decreased compared to baseline. Reduction in the exacerbation rate ranged from 11 to 50% during follow-up. In progressive MS patients, disease evolution during the trials was similar to that observed during the natural course of the disease.	Randomized placebo-controlled trials, 953 patients.	La Mantia et al. (1996)[b]
Ulcerative colitis	Placebo remission rate was 9.1% with a placebo benefit rate of approximately 26.7%.	38 double-blind placebo-controlled trials.	Ilnyckyj et al. (1997)[a]

[a] Meta-analysis.
[b] Review.

Placebo is geen panacee

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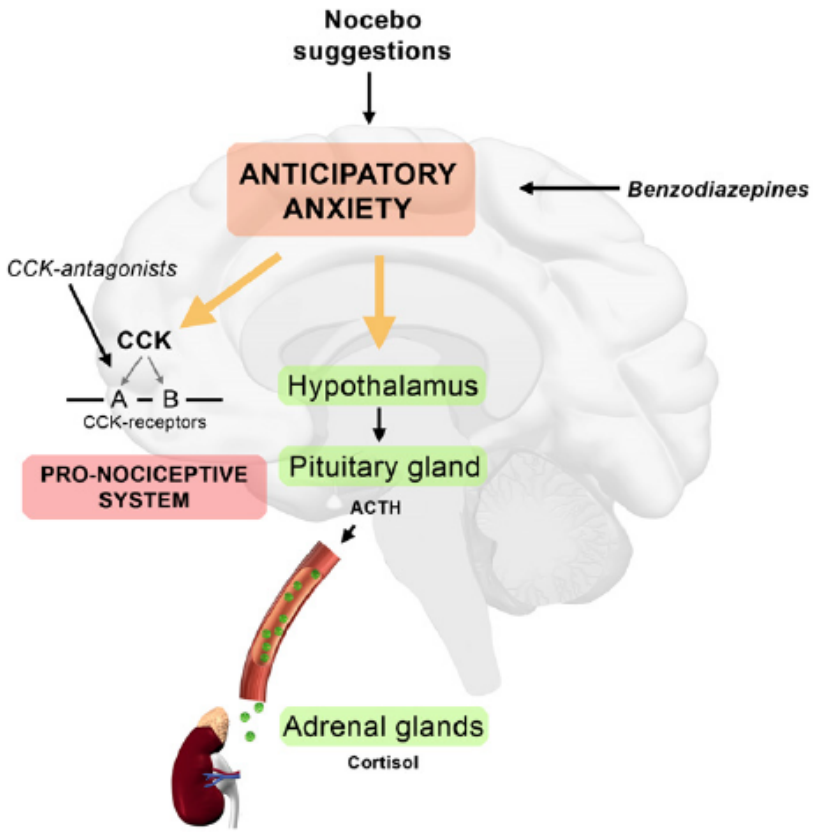
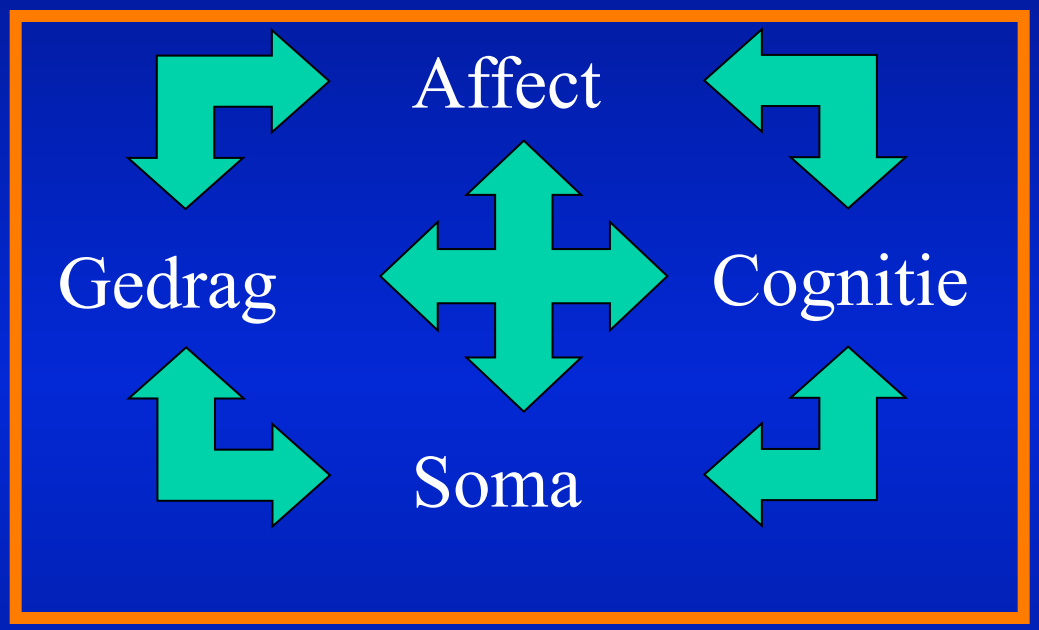


Figure 3. Mechanisms of the Hyperalgesic Nocebo Effect

Nocebo suggestions induce anticipatory anxiety, which activates two independent pathways, the hypothalamus-pituitary-adrenal (HPA) axis on the one hand and a CCK-ergic pronociceptive system on the other hand. Benzodiazepines act on anxiety, thus blocking both the HPA hyperactivity and the CCK pronociceptive system. In contrast, CCK antagonists act on the pronociceptive system only, thus preventing nocebo hyperalgesia but not HPA-hyperactivity (Benedetti et al., 2006). Note: the main propose of this sketch is to focus on neural substrates of the hyperalgesic nocebo effect which, in this case, takes precedence over anatomical accuracy.

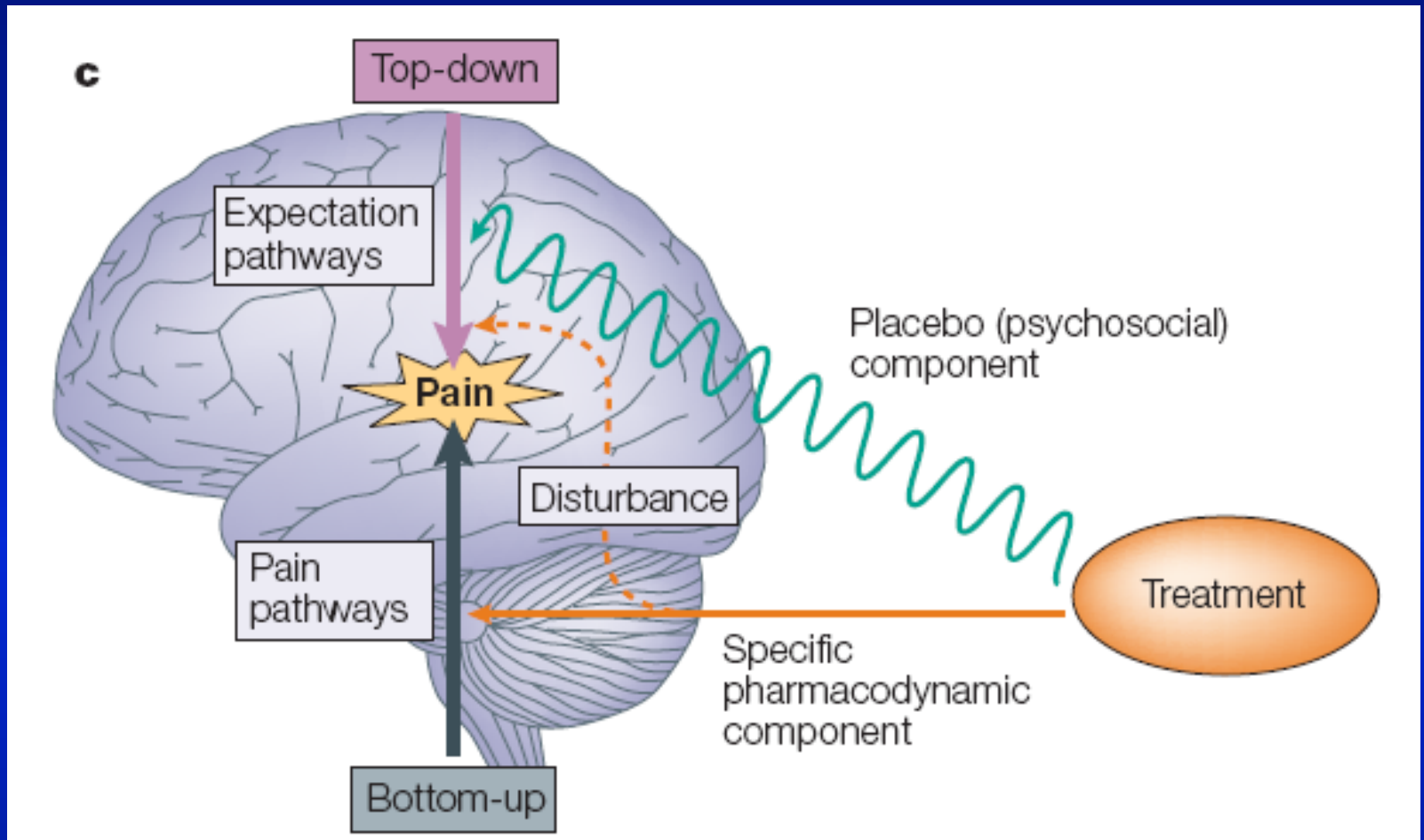
Nocebo effect

Vier, het Leven



Neuro
Fysiologisch
Onderzoek

‘Stof zijt gij, en tot stof zult gij wederkeren’


c
Top-down
Expectation pathways
Pain
Disturbance
Pain pathways
Bottom-up
Placebo (psychosocial) component
Treatment
Specific pharmacodynamic component

vereniging voor filosofie en geneeskunde

Jaarcongres Vereniging voor Filosofie en Geneeskunde

Placebo

Filosofische reflecties op een vreemde eend in de geneeskunde

zaterdag 16 oktober 2010, 10.00 – 17.00 uur
Radboud Universiteit Nijmegen, Erasmusgebouw, Erasmusplein 1
(in 'de Refter' op de begane grond van het Erasmusgebouw)

10.45 uur **Jan Ravesloot** Farmacodynamiek

Jan Hindrik Ravesloot, HL Fysiologie AMC-UvA