

The Impact of Hepatitis C on the Whole Body

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Hepatitis C

- Single-stranded RNA virus
- Member of *Flaviviridae* family:

Yellow fever

Tick-borne encephalitis

Japanese encephalitis

Dengue fever

Bovine diarrhoea virus

Hepatitis G / GVB-C

GBV-A

GBV-B

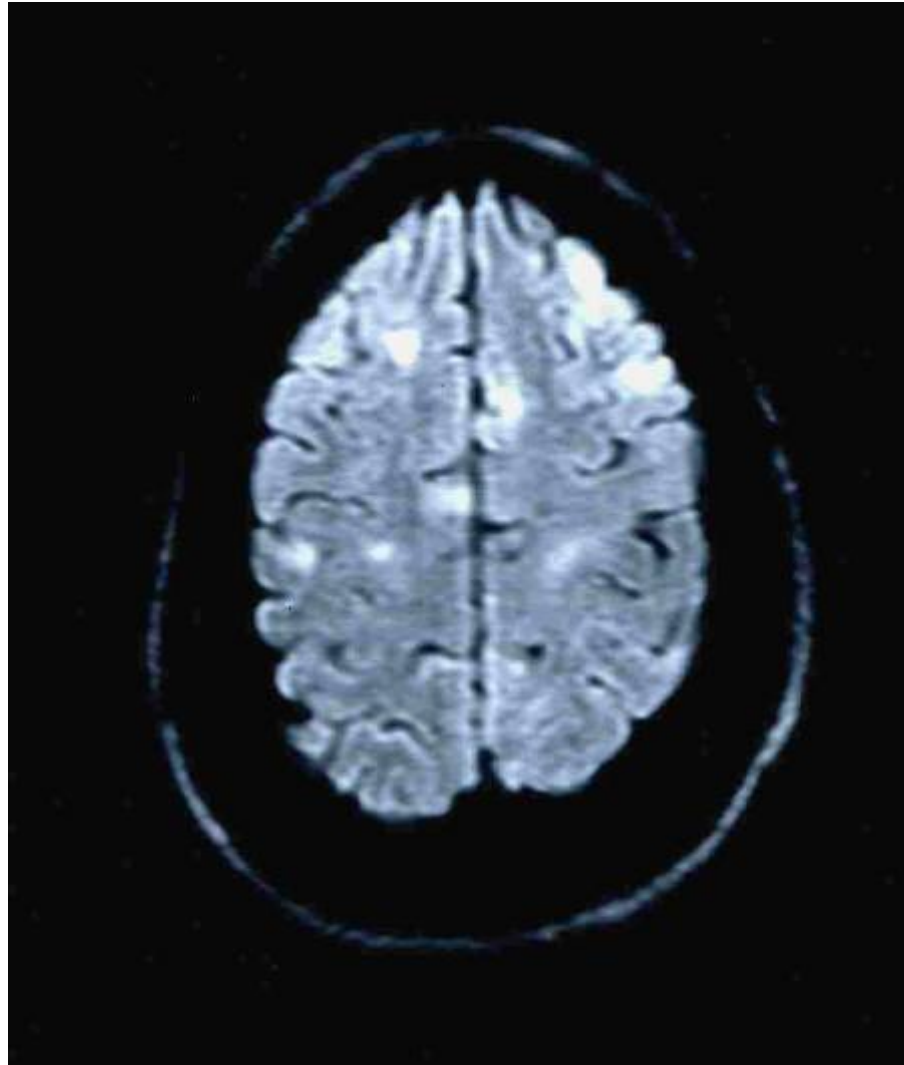
Central Nervous System manifestations:

- Vasculitis
- Cryoglobulinaemia
- Hepatic encephalopathy

- **Neuropsychological symptoms – even in minimal or absent liver disease**

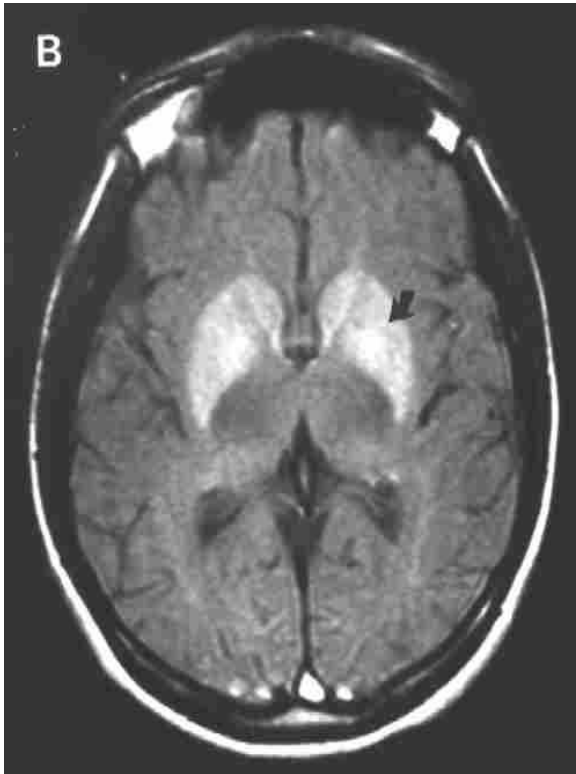
Vasculitis

- **widespread
white matter lesions**

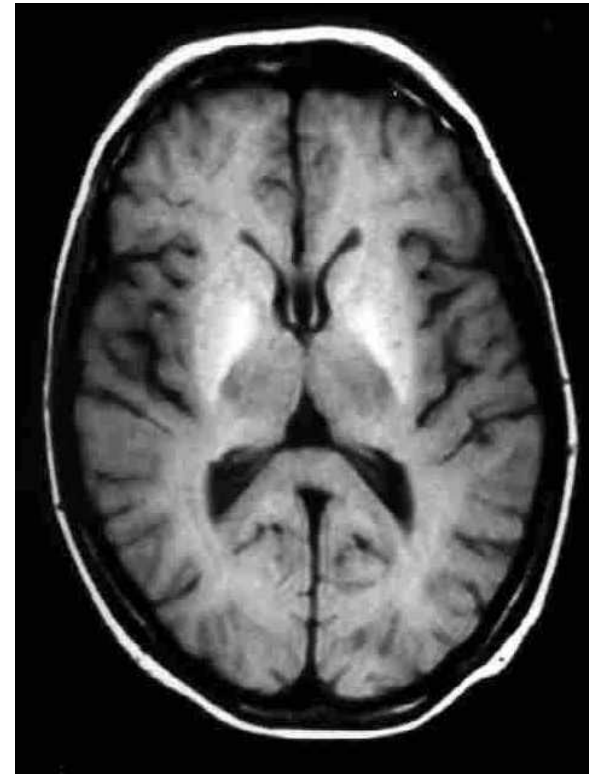


Hepatic encephalopathy

- hyperintensity in basal ganglia



T₁- weighted



Magnetisation transfer

Manganese deposition

Neuropsychiatric Symptoms

Fatigue, weakness, tiredness

Joint pain, muscle pains, arthritis

Memory loss and mental confusion - (Brain Fog)

Skin problems - ie: dry, itchy, rashes, spots

Depression, anxiety, irritability, mood swings

Indigestion, nausea, vomiting, gas

Sleep disturbances, insomnia

Pain or discomfort in the abdomen

Chills, sweating, hot or cold flashes

Eye or eyesight problems - (Blurred Vision/dry eyes)

Sensitivity to heat or cold, sweating

Vertigo, dizziness, coordination problems

Headaches

<http://therefinersfire.tripod.com/hepc.html>

CNS Involvement in HCV Infection

Fatigue

- commonest extrahepatic manifestation
- improves with treatment *(Cacoub et al. J. Hepatol. 2002)*
- multidimensional and multifactorial symptom

Epidemiology of Depression in HCV-Infected Patients

Symptoms, %	Chronic HCV-Infected Patients	General Population
Depression	23-44%	Up to 12%
Anxiety	15-37%	6%
Fatigue*	20-80%	11-45%

*Broad range due to different assessment instruments.

Coughlan B, et al. Br J Health Psychol. 2002;7:105-116.

Depression:

- Depression/Anxiety related to diagnosis and not being treated

M Kraus et al *Psychosomatics* 2000

- 309 patients completed depression questionnaire prior to HCV Antibody testing

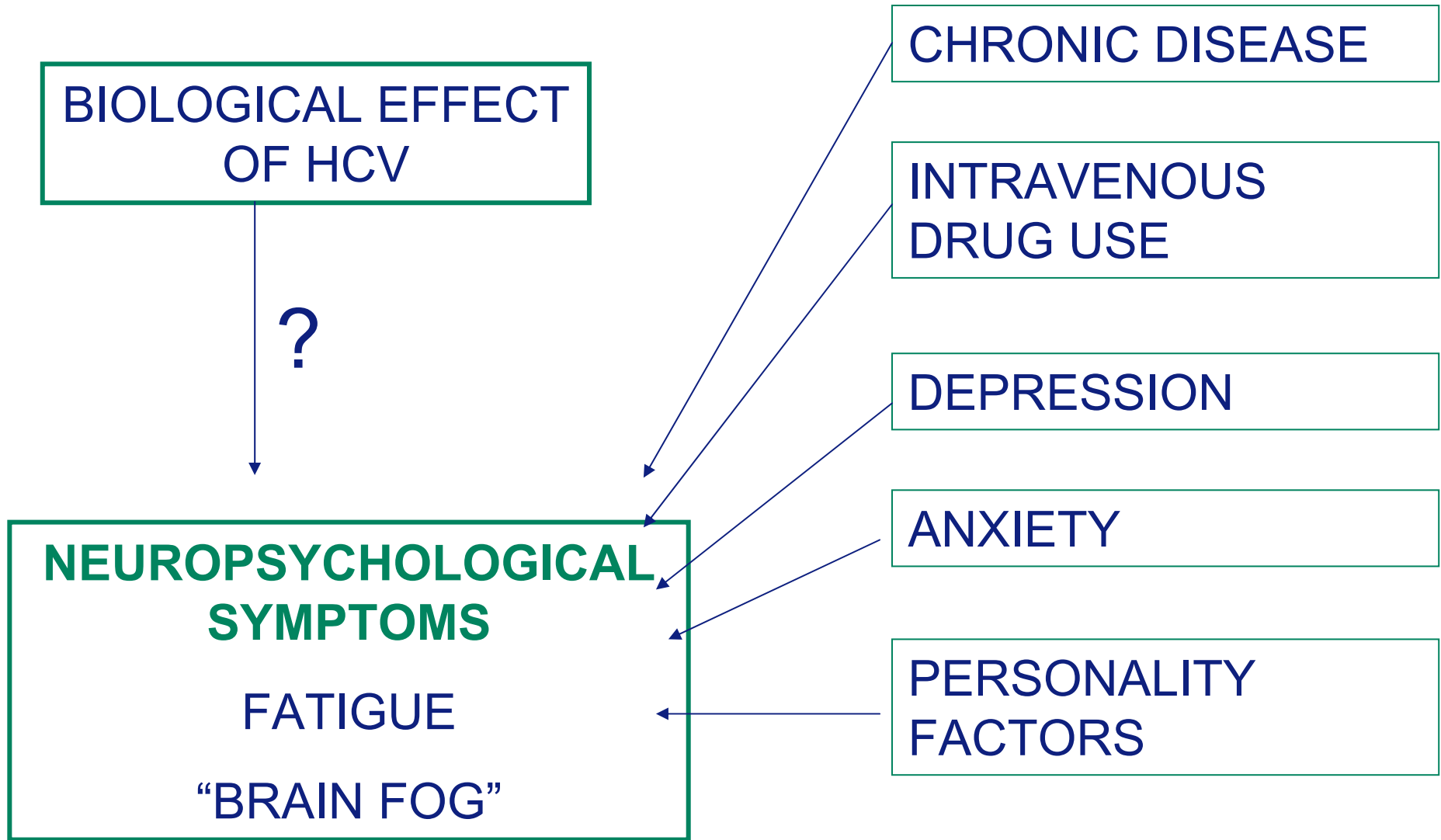
Significant depressive symptomatology in all patients

57.2% HCV+ve

48.2% HCV-ve

Johnson et al *Am J Gastroenterol* 1998

CNS Involvement in HCV Infection



BIOLOGICAL EFFECT OF HCV

?

NEUROPSYCHOLOGICAL SYMPTOMS

FATIGUE

“BRAIN FOG”

CHRONIC DISEASE

INTRAVENOUS DRUG USE

DEPRESSION

ANXIETY

PERSONALITY FACTORS

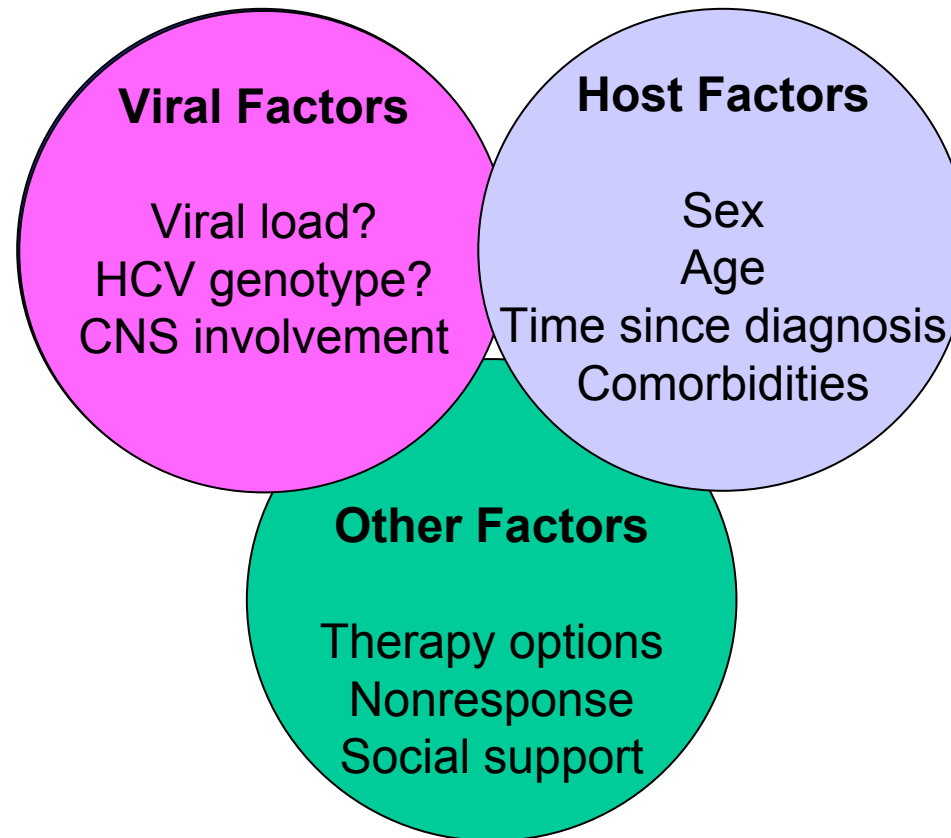
Prevalence of HCV in Risk Groups

Population	Prevalence
General population	up to 1.8%
Psychiatric population	6.7% to 8.5%
Intravenous drug users	30.0% to 98.0%

1. Williams I. Am J Med. 1999;107:2S-9S.
2. Dinwiddie SH, et al. Am J Psychiatry. 2003;160:172-174.
3. Diamantis I, et al. J Hepatol. 1997;26:794-797.
4. Yates WR, et al. Depress Anxiety. 1998;7:188-193.
5. Loftis JM, et al. Drugs. 2006;2:155-178.

Factors Possibly Influencing Depressive Symptoms in HCV

Kraus MR, et al. Psychosomatics. 2000;41:377-384. Loftis JM, et al. Drugs. 2006;2:155-178.
<http://www.who.int/mediacentre/factsheets/fs265/en/> Accessed Jul 17 2007.

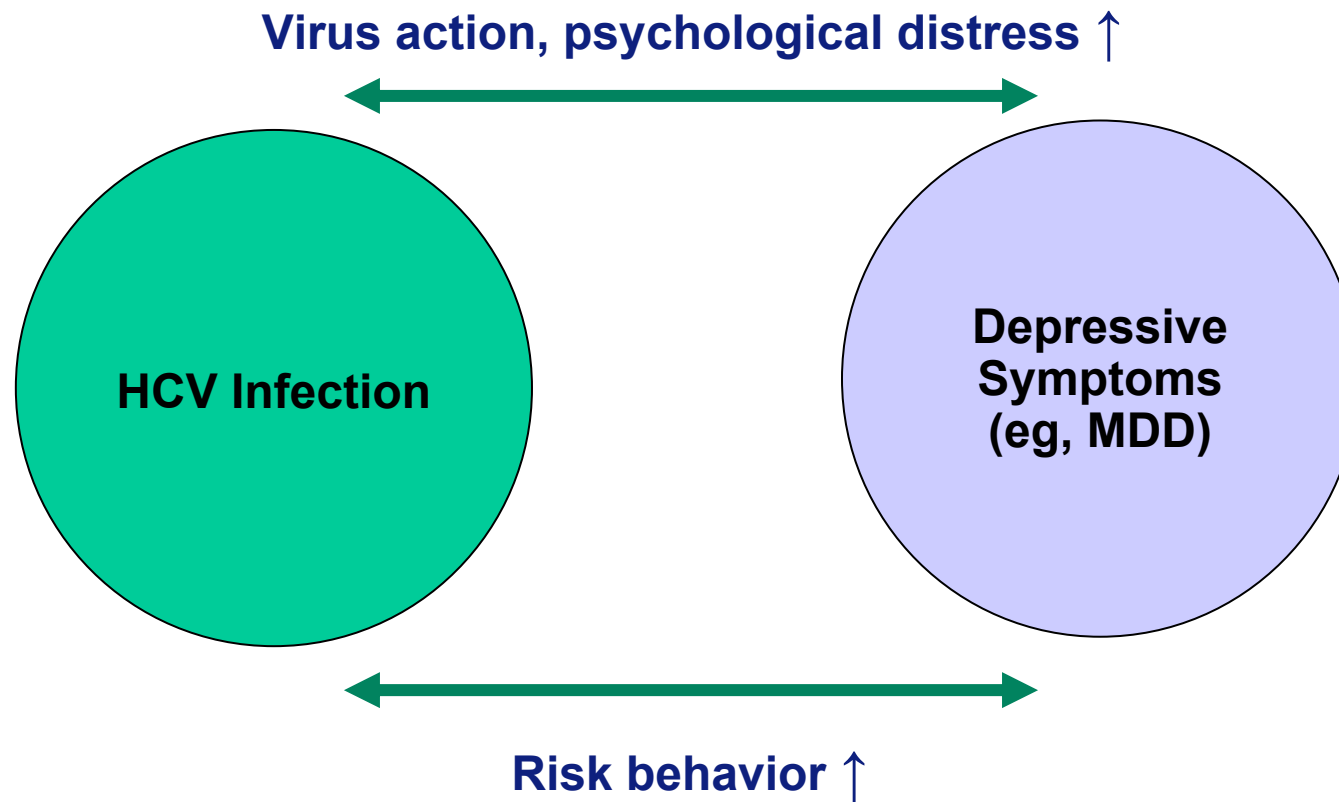


Putative Mechanisms of Depression in HCV Infection

- Patients with depression may show increased risk behaviour for HCV transmission
 - Increased risk for drug use/higher-risk drug use in patients with depression and MDD
 - Depressive disorders and PTSD associated with unsafe or more unsafe sex practices
- Concentration of higher prevalence via selection process

Angelino A, et al. Int Rev Psychiatry. 2005;17:471-476.

Interrelationships Between HCV Infection and Depression



Putative Mechanisms of Depression in HCV Infection

- Chronic HCV leads to high degree of psychological distress (stigmatization ↑, anxiety ↑, quality of life ↓)
- Reduced quality-of-life measures may account to some extent for the increase in depressive symptoms observed

→ HCV-linked depression as “reactive depression”

Angelino A, et al. Int Rev Psychiatry. 2005;17:471-476.

Evidence for Direct Action of HCV Infection on CNS

- There is evidence that HCV infection itself affects CNS^[1-3]
 - Fatigue and depression^[4,5]
 - Mild neurocognitive dysfunction^[6,7]
 - More cognitive impairment in HCV/HIV coinfection than in HIV infection^[8-10]

1. Angelino A, et al. *Int Rev Psychiatry*. 2005;17:471-476. 2. Bonaccorso S, et al. *Psych Res*. 2001;105:45-55. 3. Forton D, et al. *AIDS*. 2005;19:S53-S63. 4. Foster G. *J Hepatol*. 1999;31(suppl 1):250-254. 5. Singh N, et al. *Transplantation*. 1999;67:69-72. 6. Forton DM, et al. *Hepatology*. 2002;35:433-439. 7. Hilsabeck RC, et al. *Hepatology*. 2002;35:440-446. 8. Ryan E, et al. *Neurology*. 2004;62:957-962. 9. Letendre SL, et al. *AIDS*. 2005;19(suppl 3):S72-S78. 10. Richardson JL, et al. *AIDS*. 2005;19:1659-1667.

CNS Involvement in HCV Infection:

What to Measure?

- Cognitive function
- Brain Imaging
- Neurophysiology

Cognitive Assessment

Battery	Test	Function	Index
CDR	Simple reaction time	Attention	Speed
	Choice reaction time	Attention	Speed
	Digit vigilance	Attention	Speed
			Accuracy
	Spatial memory	Working memory	Speed
			Sensitivity index
	Numeric working memory	Working memory	Speed
Sensitivity index			
Paper	Number connection test A	Working memory Motor	Time (>37 seconds)
	Number connection test B	Working memory Motor	Time (>81 seconds)
	Digit symbol substitution test	Working memory Motor	Number correct (<55)

Impaired if 3 or more indices differed from age matched reference mean by 1SD or more

Impaired if 2 or more indices differed from reference mean by 1SD or more

Forton et al Hepatology 2002

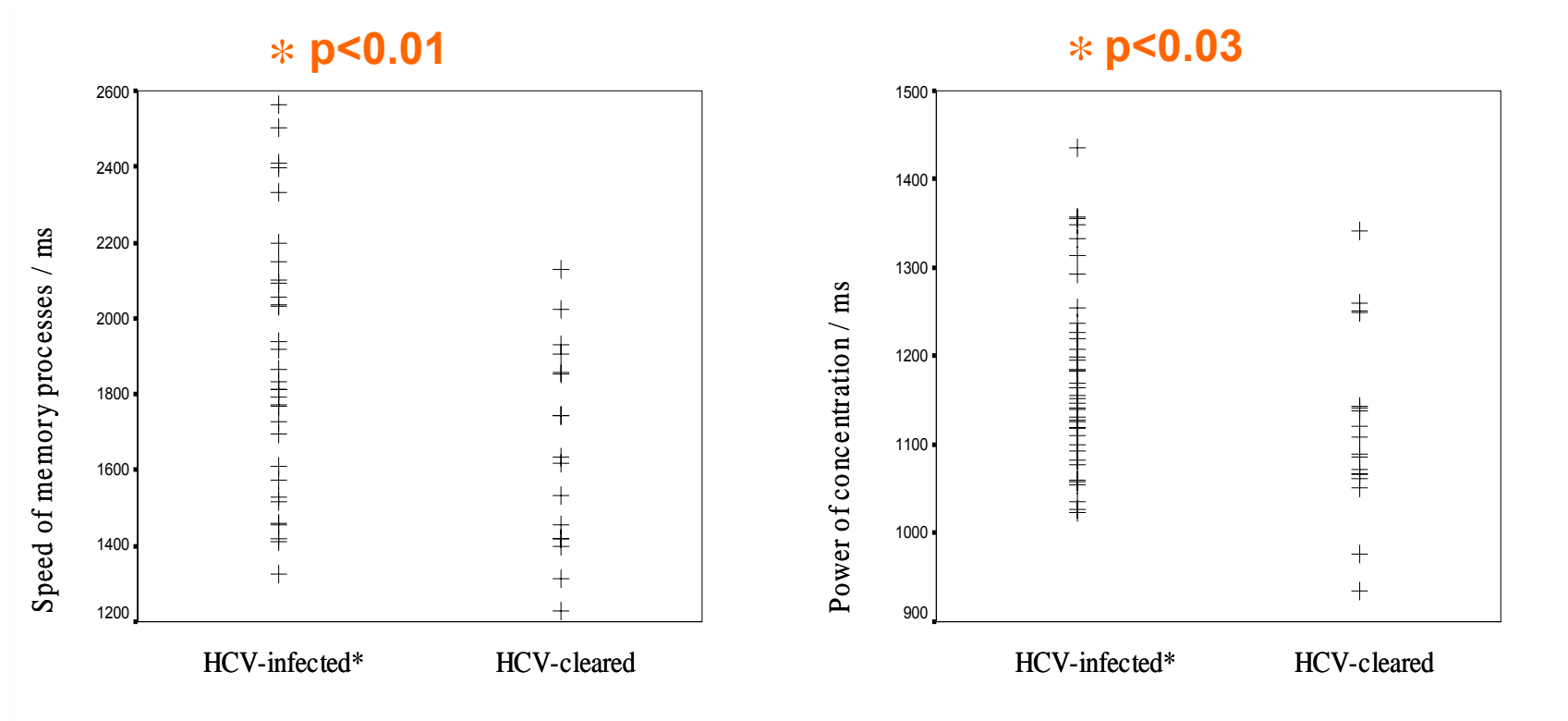
CNS Involvement in HCV Infection

HCV PCR+ve	HCV PCR-ve	
2.0 [0-6]	0.5 [0-4]	p=0.009

HCV PCR+ve patients were impaired on **more** cognitive tasks than PCR-ve patients.

- There were no associations with
- major drug history
- mood
- fatigue
- health-related quality of life

HCV viraemic patients were impaired in the domains of attention, concentration and working memory



Speed of memory processes / ms

Power of concentration / ms

*p=0.001 v controls

CNS Involvement in HCV Infection

		mean	SD	p
Beck depression inventory	HCV+ve	12.8	8.6	.006
	HCV-ve	6.6	9.2	
HAD depression	HCV+ve	6.2	3.7	.003
	HCV-ve	3.0	3.9	
HAD anxiety	HCV+ve	8.6	4.2	.039
	HCV-ve	5.8	4.3	
Physical fatigue	HCV+ve	22.1	5.2	.007
	HCV-ve	17.2	5.8	
Mental fatigue	HCV+ve	10.6	3.0	.028
	HCV-ve	8.4	2.8	

Cognitive studies in chronic HCV infection

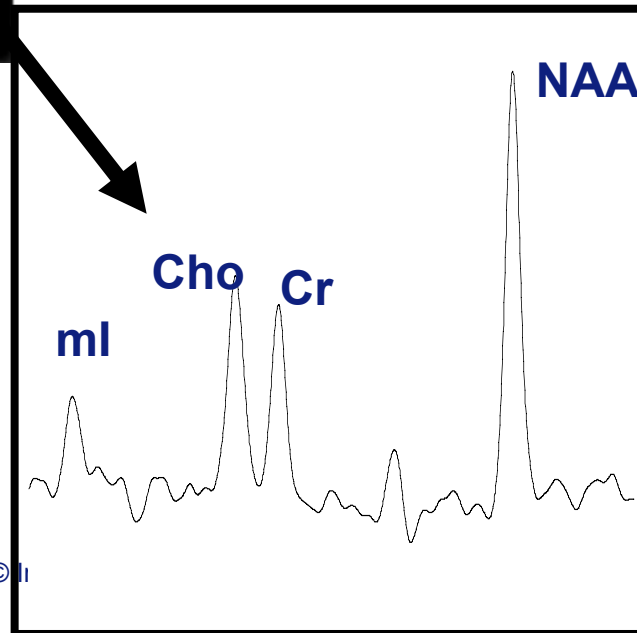
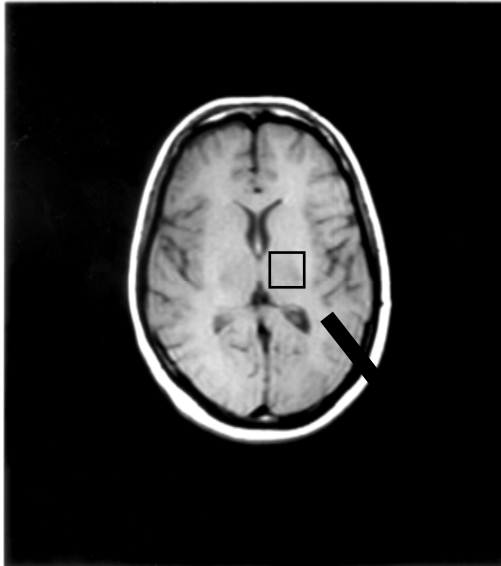
Summary

- HCV PCR+ve individuals perform worse than PCR-ve individuals on cognitive tasks
- History of intravenous drug usage, depression or severity of liver disease is non-contributory

Cognitive assessment – summary

- Mild impairments of attention, concentration
- Only evident in a proportion of patients

Normal ^1H MR Spectrum of the Brain



NAA

-N-acetylaspartate

marker of neuronal integrity

Cho - Choline

marker of cell membrane turnover

Cr – Creatine

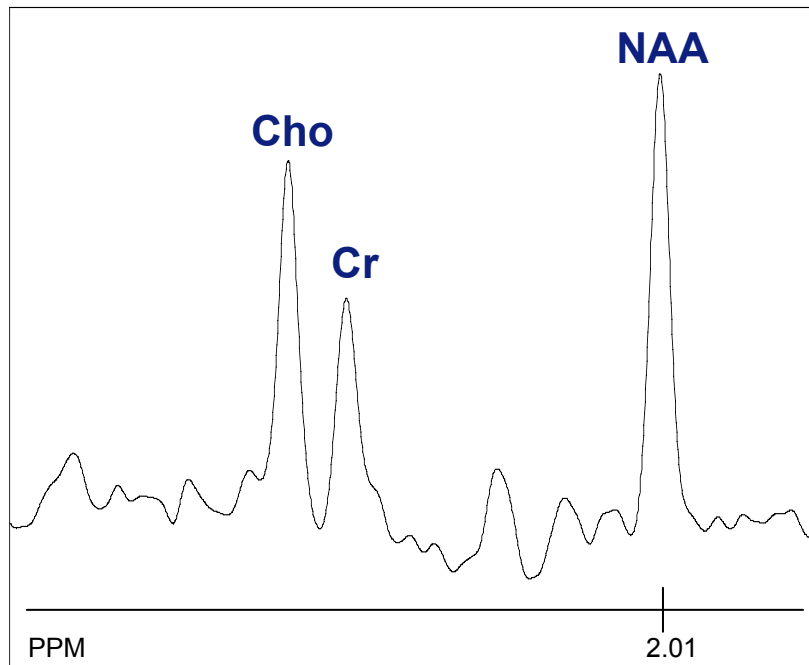
ml – Myo-inositol

cerebral osmolyte

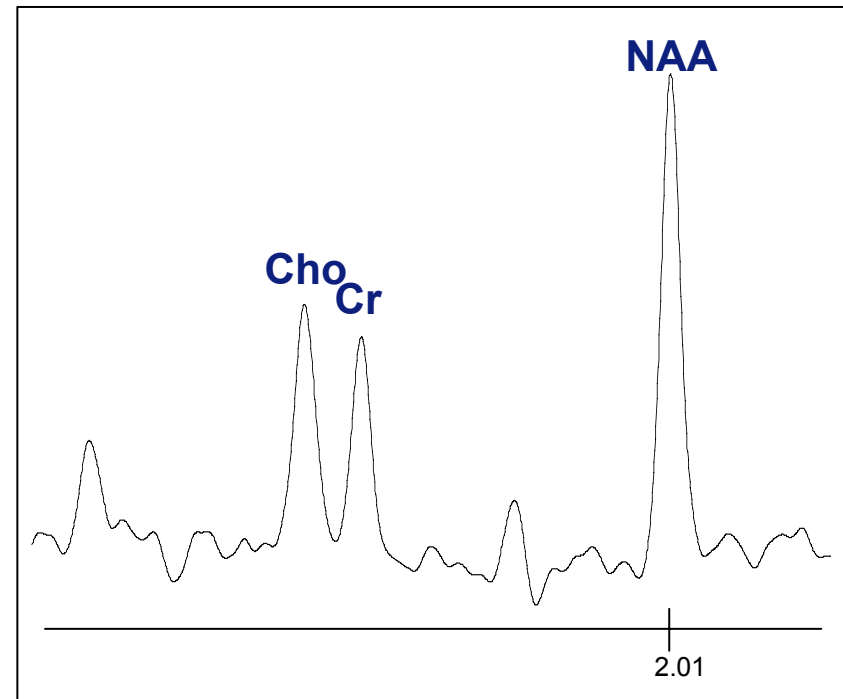
CNS Involvement in HCV Infection: What to Measure?

Elevated mean **Cho/Cr** ratio in the basal ganglia and white matter in HCV patients compared to normals and HBV patients

Forton et al Lancet 2001



Patient



Volunteer

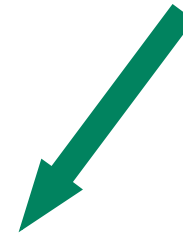
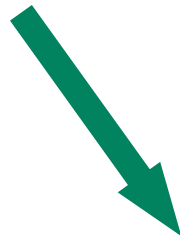
CNS Involvement in HCV Infection: What to Measure?

- Cerebral metabolite abnormalities in HCV infected patients were unrelated to a history of intravenous drug abuse
- Metabolite abnormalities similar to HIV
basal ganglia/white matter > grey matter

(Meyerhoff - Neurology 1999)

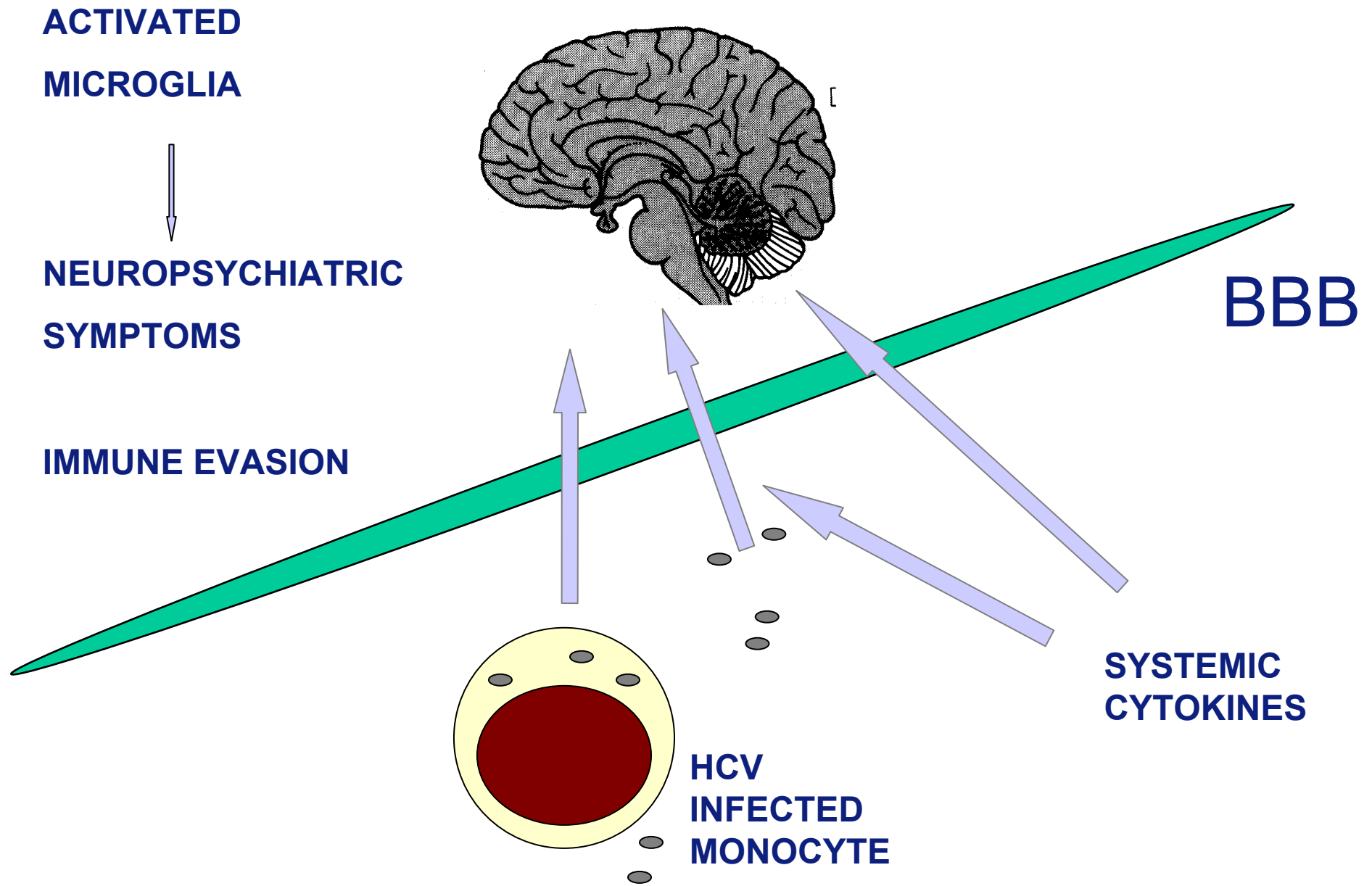
**Transfer of
systemically-derived
cytokines across the
BBB ?**

**HCV infection of the
CNS ?**

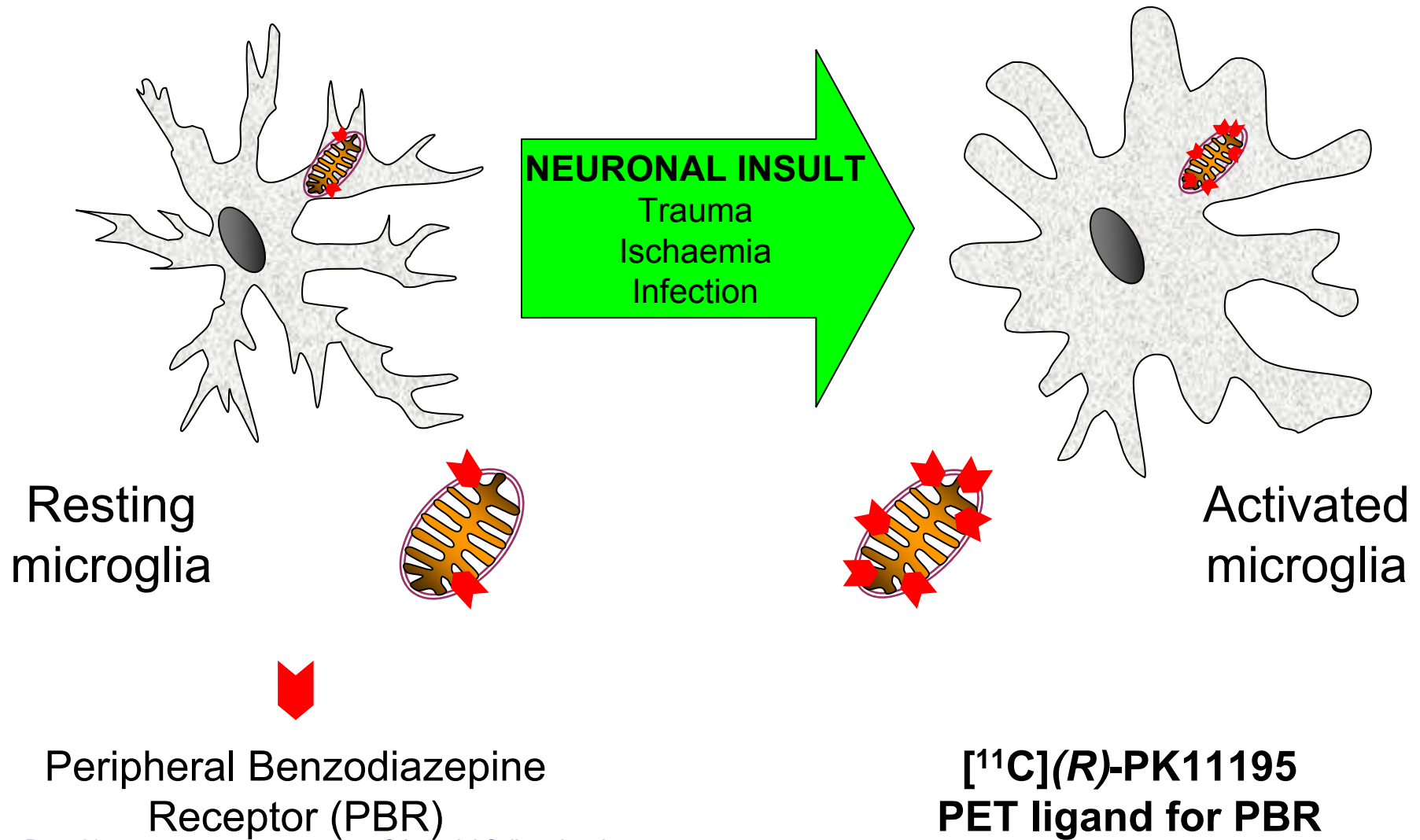


**In patients with biopsy-proven mild chronic
hepatitis C:**

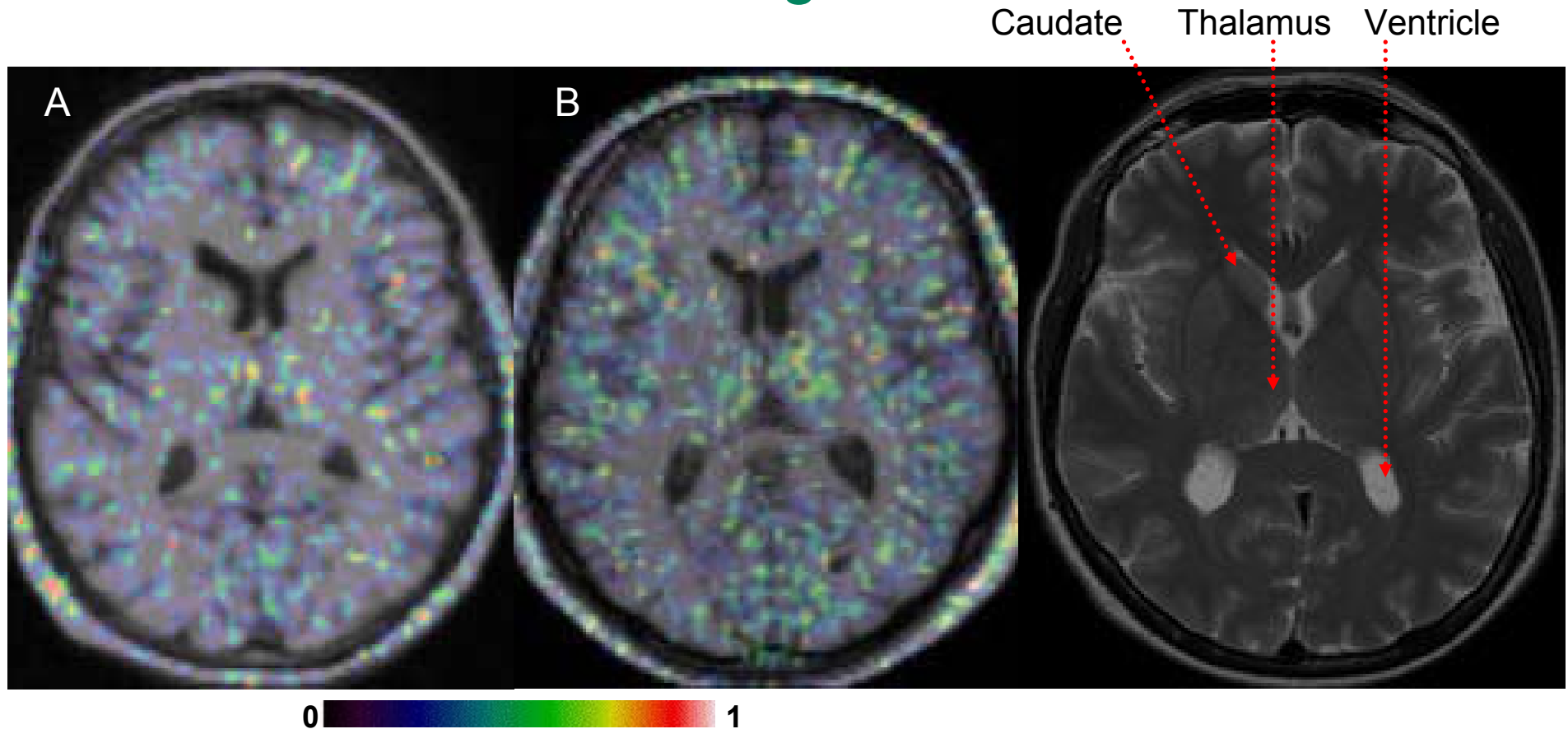
- Neurocognitive abnormality**
- Abnormal brain metabolism**



Microglial Activation



PET images



Axial PET image taken at the level of the basal ganglia from a healthy volunteer (A) and patient with mild hepatitis C (B). In the patient (B) binding is increased in the thalamus, while the healthy control (A) only shows constitutive PK11195 binding. Image C represents a T₂ MR image from the same axial level.

Demonstration of HCV replication in brain matter

Detection of negative strand RNA by RT-PCR

Detection of HCV negative-strand sequences in *post-mortem* brain tissue

Radkowski et al. J Virol 2002

Vargas et al. Liver Transpl. 2002

Summary and Conclusions

- Depression is significantly more prevalent in chronic HCV patients than in the general population
- Chronic HCV leads to high degree of psychological distress (stigmatization ↑, anxiety ↑, quality of life ↓)
- There is evidence that HCV affects CNS both directly and indirectly

Acknowledgements



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