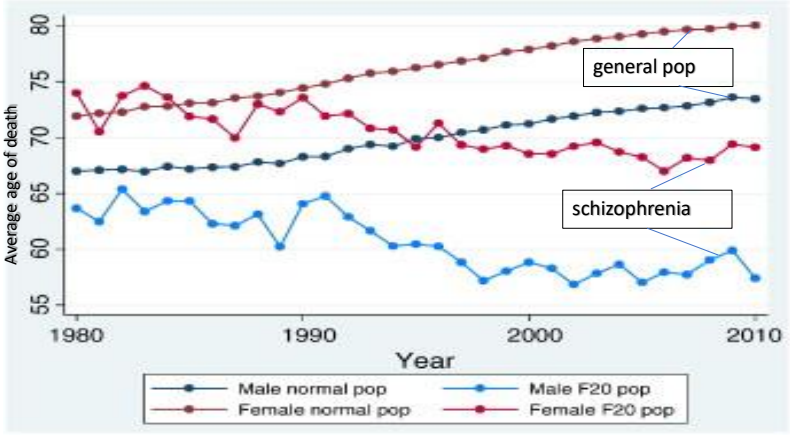
Declaration of interest

- **received investigator-initiated research funding by Gilead and Lundbeck.**
- **acted as a consultant to Janssen.**

Reduced life expectancy in severe mental illness



Nielsen et al., Schiz Res, 2013

Reduced life expectancy in severe mental illness

Increased co-morbid illness (even if medication and lifestyle effects are controlled for)

- Cardiovascular disease: 27% vs 17% gen pop *(Bresee et al., Schizophr Res 2010)*
- Metabolic syndrome: 2x increased prevalence *(e.g. Li et al., J Clin Psychiatry 2019)*
- Respiratory disease, autoimmune disorders, some cancers

Lifestyle and medication mediators

- Smoking (58%-71%), alcohol (39%-58%), illicit drugs (41%-63%; cannabis users: 38% daily use) **source: Australian national survey 2010*
- Sedentary Lifestyle, nutritional deficits *(Newcomer et al., 2007)*
- Medication adverse effects, particularly 2nd generation antipsychotics *(BUT: FIN-11 study Lancet 2009)*
- Abolishment of psychiatric inpatient beds, and inadequate replacement with community based services

Reduced life expectancy in severe mental illness

Barriers to clinical care:

People with with schizophrenia and other severe mental disorders:

- More often present to GPs, but are less frequently diagnosed with CVD or COAD than general population *(Oud et al., 2010)*
- Have a lower rate of general health checks by GPs *(Roberts et al., 2007; Mai et al., 2011)*
- Have a lower prescription rate of lipid-lowering and antihypertensive medications *(Mitchell and Lord 2010; Lahti et al., 2012)*
- Have a lower rate of cardiac hospitalization and fewer invasive cardiac procedures than the general population *(Laursen and Nortdentoft, 2011, Mitchell and Lawrence, 2011)*

High rates of HCV infection in severe mental illness

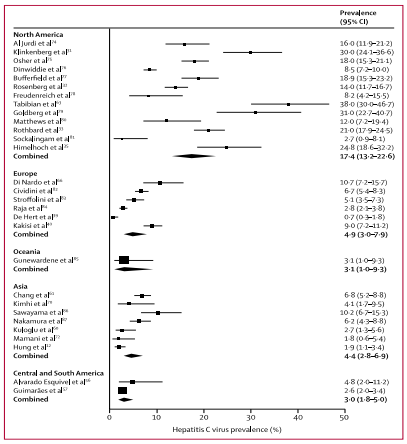


Figure 4: Prevalence of hepatitis C virus in people with serious mental illness

Hughes et al. Lancet Psychiatry 2016; 3: 40–48

Meta-analysis – Pooled prevalence:

USA: 17.4%
Europe: 4.9%
Oceania: 3.1%
Asia: 4.4%
Central/South America: 3%

General population: 1%

High rates of HCV infection in severe mental illness

Australian data (1)

Ramachandran et al, Journal of Hepatology 2018, 68, S105–S364

- 4 psychiatric inpatient units (SA) 2016-2017
- 262 patients screened
- Period prevalence of HCV antibody 11% (28/262)
- HCV RNA 6% (16/262)

- 8 initiated on DAAs (50%)
- 2 achieved sustained virological response (SVR)
- 4 await SVR
- *"The remaining eight patients have proven difficult to engage"*

High rates of HCV infection in severe mental illness

Australian data

Western Sydney Local Health District

	Screened	HCV RNA Positive	Treated or undergoing treatment
Inpatient Mental Health *Cumberland Hospital*	290	18 (20%)	12 (66%)
Community Mental Health *9 sites across WSLHD*	331	12 (3.6%)	1 (8%)

Data courtesy of Prof. Jacob George & Kristen McKee

High rates of HCV infection in severe mental illness

Australian data

Northern Adelaide Local Health Network

	Screened	HCV RNA Positive	Treated or undergoing treatment
Inpatient Mental Health *Lyell McEwin Hospital*	113	7 (6.2%)	4 (57%)
Community Mental Health *2 sites across NALHN*	38 (but 61 blood forms given)	4 (10.5%)	4 (100%)

Data courtesy of Lucy Ralton and Michelle Bown

HCV in severe mental illness – summary and conclusios

- The **prevalence** of HCV infection in people with severe mental illness is **4-20 times higher** than in the general population
- Reliable detection of cases requires ***assertive screening programmes within mental health services***
- The **uptake of treatment in identified cases is often poor** – multidisciplinary and collaborative efforts across Health Networks are required to improve this
  - *universal screening within mental health services*
  - *collaboration psychiatry, hepatology, infectious diseases*
  - *In-reach of viral hepatitis nurses*
  - *proactive treatment guidance*

HCV and brain health - mechanisms

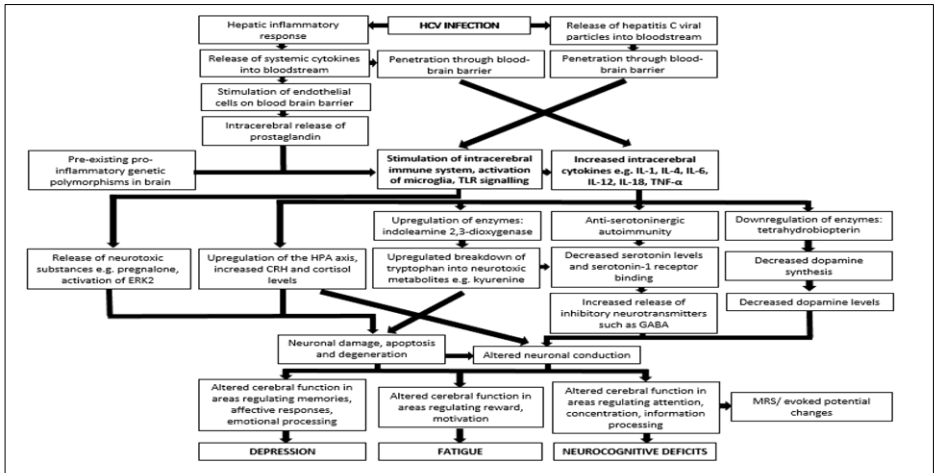
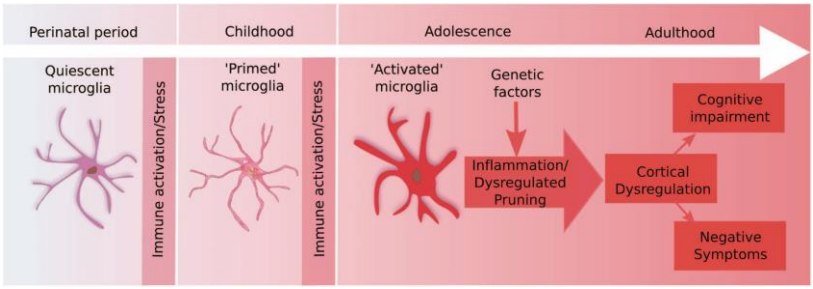


Fig. 2 overview of HCV mechanisms causing depression, fatigue and neurocognitive deficits through intracerebral neurobiological changes. *CRH* corticotropin-releasing hormone, *ERK2* extracellular signal-regulated kinase 2, *GABA* gamma-aminobutyric acid, *HCV* hepatitis C virus, *HPA* hypothalamic–pituitary–adrenal, *IL* interleukin, *MRS* magnetic resonance spectroscopy, *TLR* toll-like receptor

Yeoh et al . Hepatology International (2018) 12:294–304

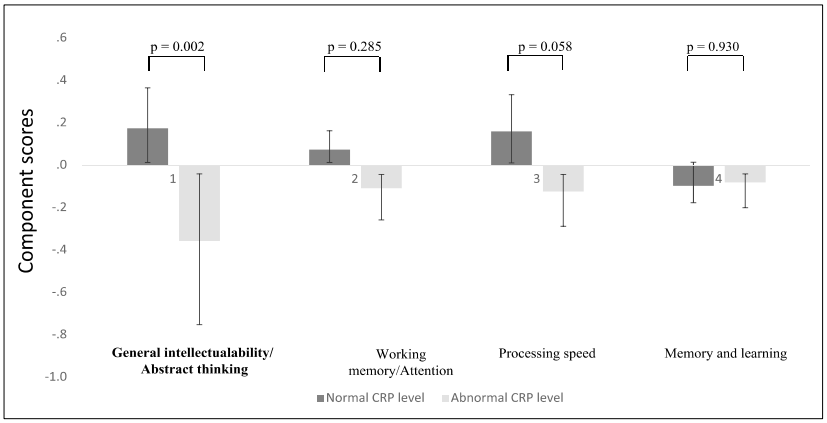
Inflammation in Schizophrenia: microglia & the two hit hypothesis



Howes and McCutcheon Transl Psychiatry (2017) 7, e1024

- Perinatal activation of microglia leads to a primed state
- Stress in adolescence (e.g. trauma) triggers pathological overactivation
- Medication-naive first-episode psychosis patients have increased expression of microglia (M1) activation associated pro-inflammatory cytokines: IL-1B, IL-6 and TNFa.
- peripheral cytokine levels are associated with reductions in hippocampaland prefrontal cortex volumes.

Inflammation and cognition in schizophrenia



N=369, stable patients, Wechsler Adult Intelligence Scale (WAIS)

Bulzacka et al., Schizophrenia Bulletin 2016 42(5) 1290–1302

Treating inflammation in schizophrenia

TABLE 3 | Outcomes of meta-analyses of randomized controlled trials (RCTs) on minocycline and NSAID.

	N RCTs	Subjects	Treatment duration (weeks)	Total symptoms (PANSS total score or BPRS)	Positive symptoms (PANSS positive subscale or BPRS)	Negative symptoms (PANSS negative subscale or SANS)	General symptoms (PANSS general subscale)
Minocycline							
Sommer et al. (minocycline) (38)	4	182 drug–166 placebo	36 ± 18.8	SMD 0.22			
Oya et al. (minocycline) (39)	4	173 drug–157 placebo	25 ± 19.1	SMD 0.70*	SMD 0.26	SMD 0.86**	SMD 0.50*
Solmi et al. (minocycline) (40)	6	215 drug–198 placebo	19.7 ± 17.0	SMD 0.59*	SMD 0.22	SMD 0.76** (PANSS); SMD 0.60** (SANS)	SMD 0.44*
Xiang et al. (minocycline) (41)	8	286 drug–262 placebo	18.5 ± 13.4	SMD 0.64**	SMD 0.22*	SMD 0.69**	SMD 0.45*
NSAID							
Sommer et al. (NSAID) (36)	5	*N* = 264					
Nitta et al. (aspirin) (37)	2	133 drug–137 placebo	14 ± 2.8	Hedges *g* 0.29*			
Nitta et al. (celecoxib) (37)	6	255 drug–245 placebo	7.7 ± 2.1	Hedges *g* 0.21			
Sommer et al. (aspirin) (38)	2	133 drug–137 placebo	14 ± 2.8	Hedges *g* 0.30**			
Sommer et al. (celecoxib) (38)	5	236 drug–226 placebo	7.2 ± 2.4	Hedges *g* 0.15			
Zheng et al. (celecoxib) (42)	8	316 drug–310 placebo	8.3 ± 2.3	SMD 0.47**	SMD: 0.50**	SMD 0.32	SMD 0.35*

SMD, standardized mean difference; PANSS, Positive and Negative Syndrome Scale; SMD, standard mean deviation; BPRS, Brief Psychiatric Rating Scale.
**Sig at p = 0.05.*
***Sig at p = 0.01.*

De Picker et al. (2017) Front. Psychiatry 8:238.

Cognitive effects of treating HCV

Kleefeld et al. Neurology 2017; 88 (7)

- HCV patients **without** mental illness
- Treatment regimens:
  - ombitasvir/paritaprevir/ritonavir + ribavirin (n = 2)
  - ledipasvir/sofosbuvir (n = 9)
  - sofosbuvir + ribavirin (n = 1)

- **significant medium to large effect sizes of cognitive improvement (d= 0.20 to d= 1.79)**
  - visual learning/memory
  - attention/working memory
  - executive function
  - processing speed

Sofosbuvir/Velpatasvir and Mental Health Impact in people with Lived Experience and Hepatitis C infection

Smile-C Trial

Boyd M, Schubert KO, Clark SR, Matthews G & Smile-C investigator team

Smile-C: Hypothesis and Objectives

Hypothesis

Successful HCV treatment with DAA-based therapy is associated with improved neurocognitive function in people with severe mental illness.

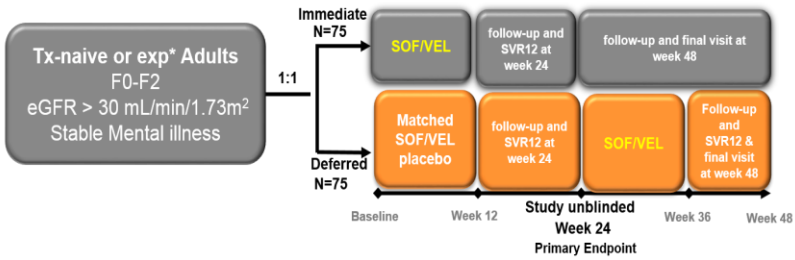
Primary objective

To investigate the effect of sustained virological response (SVR) on neurocognitive function in people with severe and enduring mental illness.

Secondary objective

To investigate whether HCV treatment with DAA based therapy is acceptable, safe and effective for people with severe and enduring mental illness.

SMILE-C study design



Baseline (week 0): Neurocognitive tests (groups 1 & 2)
Primary endpoint (week 24): SVR12 (groups 1 & 2); Neurocognitive tests (groups 1 & 2)
Secondary endpoint (week 48): SVR12 (group 2); Neurocognitive tests (group 1 & 2)

* Defined as prior exposure to PegInf, Riba, Telaprevir or Boceprevir

TRIAL SETTING/LOCATIONS	
Hospital sites	Affiliated psychiatric community services
NALHN	
Lyell McEwin Hospital	Northern Community Mental Health Service; Club 84; Wondakka; North Eastern Community Mental Health; The Gully
CALHN	
Royal Adelaide Hospital	Eastern Community Mental Health Centre
The Queen Elizabeth Hospital	Western Community Mental Health Care
SALHN	
Flinders Medical Centre Flinders Drive	Marion GP Plus Health Care Centre, Community Mental Health
Noarlunga Hospital	Noarlunga Community Health Service
Country Health SA LHN	
Mt Gambier and Districts Hospital	Rural and Remote Mental Health Service
Millicent and District	Millicent Community Health
Glenside Hospital	Flinders Terrace Community Health Service
6 Sydney Local Health District Hospitals	

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Kristen McKee

SMILE-C investigator team