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Mechanisms of cognitive dysfunction in CKD

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Abstract: Cognitive impairment is an increasingly recognized major cause of chronic disability and is commonly found in patients with chronic kidney disease (CKD). Knowledge of the relationship between kidney dysfunction and impaired cognition may improve our understanding of other forms of cognitive dysfunction. Patients with CKD are at an increased risk (compared with the general population) of both dementia and its prodrome, mild cognitive impairment (MCI), which are characterized by deficits in executive functions, memory and attention. Brain imaging in patients with CKD has revealed damage to white matter in the prefrontal cortex and, in animal models, in the subcortical monoaminergic and cholinergic systems, accompanied by widespread macrovascular and microvascular damage. Unfortunately, current interventions that target cardiovascular risk factors (such as anti-hypertensive drugs, anti-platelet agents and statins) seem to have little or no effect on CKD-associated MCI, suggesting that the accumulation of uraemic neurotoxins may be more important than disturbed haemodynamic factors or lipid metabolism in MCI pathogenesis. Experimental models show that the brain monoaminergic system is susceptible to uraemic neurotoxins and that this system is responsible for the altered sleep pattern commonly observed in patients with CKD. Neural progenitor cells and the glymphatic system, which are important in Alzheimer disease pathogenesis, may also be involved in CKD-associated MCI. More detailed study of CKD-associated MCI is needed to fully understand its clinical relevance, underlying pathophysiology, possible means of early diagnosis and prevention, and whether there may be novel approaches and potential therapies with wider application to this and other forms of cognitive decline.

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Mechanisms of cognitive dysfunction in CKD

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Abstract

Cognitive impairment is an increasingly recognized major cause of chronic disability, and is commonly found in patients with chronic kidney disease (CKD). A better understanding of the relationship between kidney function and cognition may help us to understand better other forms of cognitive dysfunction. Patients with CKD have an increased risk (compared with the general population) of both dementia and its earlier stage of mild cognitive

60impairment (MCI), with deficits in executive functions, memory and attention. Brain imaging
61in CKD patients has detected damage to white matter in the prefrontal cortex and, in animal
62models, in the subcortical monoaminergic and cholinergic systems, accompanied by
63widespread macro- and micro-vascular damage. Unfortunately, current interventions that
64target cardiovascular (CV) risk factors (anti-hypertensives, anti-platelet agents and statins)
65seem to have little or no effect on MCI-CKD, suggesting that the accumulation of uremic
66(neuro)toxins may be more important in this disorder than disturbed hemodynamic factors or
67lipid metabolism. Experimental models show that the brain monoaminergic system is
68susceptible to uremic neurotoxins and that this system is responsible for the altered sleep
69pattern commonly observed in CKD patients. Neuronal stem cells and the brain glymphatic
70system, shown to be important in Alzheimer's disease (AD), may also be involved. MCI-
71CKD needs to be studied in more detail to understand fully its clinical relevance, underlying
72pathophysiology, and possible means of early diagnosis and prevention; and whether there
73may be novel approaches and potential therapies with wider application to this and other
74forms of cognitive decline.

75

76 **Key points**

77Cognitive impairment is more common in patients with chronic kidney disease (CKD) and
78reduced renal function than in the general population.

79Brain dysfunction in CKD patients likely results from uremic (neuro)toxins interacting with
80neuronal stem cells, the brain vascular and glymphatic system, and catecholaminergic
81neurons.

82Targeting these mechanisms could potentially reduce the burden of dementia in CKD and
83might help in finding better treatments for other forms of cognitive impairment.

84

85 **Introduction**

86The widely used term 'cognitive dysfunction' has been defined in many different ways, but
87collectively refers to a combined deficit of brain processes that affect learning, memory, and
88sensory processing. It varies from mild cognitive impairment (MCI. See Box 1) to severe
89dementia, the latter characterized by a loss of independence in carrying out activities of daily
90living¹. MCI may be considered as a prodromal state before established dementia with an
91annual conversion rate of 1. 9% per year². Although MCI is inherently unstable (patients may

92progress or revert to normal cognition), some investigators consider it to be a distinct clinical
93entity³. Despite the increasing prevalence and incidence of MCI and dementia, there remains
94a lack of disease-modifying drugs and a comprehensive biological understanding of MCI, as
95well as an understanding of the mechanisms that determine the transition from MCI to
96dementia.

97A significant number of patients with chronic kidney disease (CKD) suffer from cognitive
98dysfunction, and CKD is among the strongest risk factors for MCI and dementia. When
99considering the odds ratio, a 6-year longitudinal study in the general population listed CKD
100as the third major risk factor for MCI and dementia after stroke and chronic use of anxiolytics,
101and ahead of genetic factors⁴. Cognitive impairment can already be evident at early stages of
102CKD⁵ (Figure 1). However, the relationship between the severity of CKD (based on
103estimated Glomerular Filtration Rate, eGFR) and the severity of dementia/MCI is unclear.
104When taking into account age, cognitive changes at different CKD stages may be related to
105the presence and degree of albuminuria^{6–10}. Indeed, a separate study suggests that the
106duration of kidney disease, rather than the degree of renal impairment, correlates with brain
107dysfunction. Available long-term follow-up studies in CKD patients also suggest greater
108cognitive decline in those with higher levels of albuminuria, but an unclear effect of eGFR
109^{6,11}.

110Current techniques of renal replacement therapy have different effects on cognitive
111dysfunction: hemodialysis (HD) and peritoneal dialysis (PD) can treat effectively the acute
112uremic encephalopathy seen in some non-dialyzed patients with end-stage renal failure
113(ESRF), but have little effect on MCI, although there may be a slightly better outcome with
114PD^{12,13} compared with HD. Conversely, kidney transplantation is likely to play a protective
115role, although without complete reversal to normal cognition in healthy subjects¹⁴ (Figure 1).
116Several mechanisms have been proposed to explain the brain dysfunction seen in CKD,
117particularly focusing on the vascular damage and altered extracellular *milieu* that
118accompanies CKD.

119The CKD-cognitive impairment conundrum has become a major focus of the scientific
120community, as evident from the increasing number of published meta-analyses and review
121articles (see e.g.^{15–17}). However, much of the current literature does not discuss the topic in
122the context of recent developments in neuroscience and neurology, such as neural stem cells,
123brain glymphatics or subcortical modulatory systems (e.g., dopamine and norepinephrine
124systems); furthermore, the pace of new findings is so rapid that an updated perspective can be

justified. This is an ongoing and active field of research, and new functional tools to study both the brain and kidney hold the promise of advancing our understanding of MCI-CKD. This review summarizes our current knowledge of the pathogenesis of brain lesions associated with CKD and their likely effects on cognition. The changes observed are discussed in the context of uremic neurotoxicity and vascular damage^{18,19}. We focus on brain dysfunction occurring in CKD, rather than in acute kidney injury (AKI), which has been considered in detail elsewhere²⁰. Finally, our review does not discuss depression, which is also detailed elsewhere²¹.

133

1. Epidemiology of CKD and cognitive dysfunction

With a prevalence ranging from 27% up to 62%^{18,22–24} (depending on the age and the study) MCI is more common among CKD stage 1-4 patients than in a matched non-CKD population (prevalence 11%-26%)^{22,23,25}. While MCI does not affect activities of daily living, 5-10% of those affected will eventually progress to clinical dementia²⁶. The prevalence of dementia is 8-37% among HD patients^{10,25,27–29}, 4-33% among those on PD^{25,29} and around 7-22% in kidney transplant patients^{14,30}. In contrast, the prevalence of dementia in the general population is 5% (95% CI 4. 5%–5. 7%)³¹. Most of the studies comparing the prevalence of MCI/dementia in CKD with the general population take into account age, gender and education (which may affect the estimates). In Figure 1 we summarize an estimate of the MCI trend in CKD, PD and HD patients according to kidney function and the age.

Regarding the age of onset of cognitive decline (in relation to first diagnosis) the data are scanty. In the general population the incidence rate is negligible (less than 1%) below age 65 years and then increases exponentially as a function of age (7.4% at 70 years)^{32,33}. Conversely, in kidney transplant patients the 10-year risk of dementia is 5% in those aged 55 years, but also increases linearly with age³². Similarly, the 10-year risk of dementia after HD initiation is 20% in patients aged 65 years and again increases linearly with age³⁰. In addition, data by Kurella Tamura et al³⁴ suggest a higher prevalence (about 10%) of cognitive impairment even in relatively young subjects (21-44 years) with end-stage renal failure (ESRF).

According to a 2019 study, the incidence rate for dementia per 1000 patients-years is 1.4 in the non-CKD population and 10.7 in the ESRF population³⁵. In patients with eGFR levels >60 ml/min, albuminuria, an early marker of endothelial damage and microvascular

157disease, is associated with the presence of MCI ⁸. This has been confirmed repeatedly, with
158an unclear relationship to age: some papers report a greater effect of albuminuria in older
159patients ⁷, others only in younger patients.

160Nephrologists need to be aware that a substantial proportion of their patients may have mild
161to severe forms of cognitive impairment, and the neurologist also needs to be cognizant of the
162presence and form of cognitive deficits occurring in patients with CKD. Indeed, MCI-CKD
163might be qualitatively different from the MCI seen in the general population in respect of its
164neuropsychological test patterns (e.g., better performance on Trail Making Test B) and EEG
165studies ³⁶, MRI findings³. Ideally, current guidelines for MCI diagnosis and management
166should require an assessment of kidney function as part of the routine neurological work-up ³⁷.

167

168 **2. Cognitive domains and correlated brain features in CKD**

169“Cognitive decline” is an umbrella term that encompasses all forms of dementia (such as AD),
170delirium or confusional states, and mild cognitive slowing. It should be noted that the terms
171“cognitive impairment” and “dementia” are often used as synonymous, the first being
172introduced as a non-stigmatizing term ³⁸. Cognitive function is tested by various means,
173including by recalling memorized lists of numbers or drawing an object on request, or
174naming a figure. Cognitive impairment is subdivided into specific cognitive domains, such as
175attention, memory, visuospatial, language skills and executive functions (see Box 2).

176 **2. 1. Attention**

177Patients with CKD show inattention (see Box 2) and impaired inhibitory control ³⁹, which is
178the inability to suppress ongoing and inappropriate actions. Indeed, a young population with
179mild-moderate CKD has poor performance in a test of attention and inhibitory control, which
180depends on the duration of disease, rather than the severity of CKD ³⁹. Furthermore, CKD
181patients have a slower EEG reaction when paying attention to a visual stimulus (termed
182“P300 wave event related potential”)⁴⁰, which was shown to be partially dependent on the
183presence of anemia ⁴¹. Transplantation does not modify the attention and inhibitory control
184performances compared with non-transplanted CKD patients ⁴². Many brain regions are
185required for attention and inhibitory control, such as the prefrontal cortex (PFC) and the
186Locus Coeruleus in the dorsal pons, which produces norepinephrine. Compared with normal
187controls, patients on HD show a reduced thickness and increased number of connections of
188the PFC ⁴³. Furthermore, PET studies also show decreased metabolic activity in this region in

ESRF patients compared with normal subjects⁴⁴. In the non-CKD population, the frontal gray matter volume is less affected in MCI⁴⁵, but can be reduced in other forms of dementia (fronto-temporal dementia, Alzheimer's Disease (AD) and Levy bodies dementia^{46,47}). An EEG study directly comparing MCI-CKD to MCI in the general population describes a more pronounced dysfunction in the frontal cortex³⁶.

Data from animal models of CKD suggest an altered activation (number of neurons active at rest, indexed by c-Fos expression) of the PFC and of the norepinephrine neurons of the Locus Coeruleus⁴⁸ (see also Figure 2), possibly due to neuroinflammation⁴⁹. Another mechanism for the effect of CKD on norepinephrine neuronal function arises indirectly from the observation of altered tyrosine metabolism, the precursor for norepinephrine⁵⁰. Interestingly, antioxidant therapies and angiotensin-converting enzyme inhibitors may reverse these changes and should be explored in future as a possible protection against MCI/dementia in CKD.

Attention deficits in CKD patients may be attributable to altered catecholamine-PFC circuitry.

2. 2. Memory

Memory storage and processing are likely to be served by different brain regions according to the type of memory (see Box 1). Both the implicit and explicit forms of memory appear to be altered by CKD⁵¹. Indeed, patients on HD compared with healthy controls had poorer scores when trying to recall a list of words (explicit memory) or images (implicit memory). The memory performance did not change when comparing before and after dialysis treatment.

The storage/retrieval of explicit memories requires the integrity of the cerebral cortex and the hippocampus and the activity of cholinergic neurons in the Meynert nucleus. In animal models, CKD induces neuronal death in the hippocampus⁵² and reduces the activity of cholinergic neurons in the Meynert nucleus⁴⁹ (Figure 2).

At the neuronal scale memories are stored as long-term modifications of their synapses. An experimental study in mice demonstrated a reduction in synaptic contacts in animals with reduced kidney function⁴⁹. Since memory traces are stored in the ordered connectivity of synaptic contacts among neurons^{53,54}, synaptic loss may underlie the reduced memory in CKD. Overall, data suggest that the interaction between cholinergic neurons and the cortex may be responsible for memory dysfunction in CKD.

2. 3. Language, visuospatial performance and executive dysfunction

Language skills are also affected in CKD, and this is the only cognitive domain linearly dependent on eGFR decline $¹⁰$. Language ability can be tested by presenting a

221 picture and asking the subject to name it (as with the Boston Naming test). Several studies
222 document poor naming performance in patients with CKD^{10,55–57}. MRI studies in CKD
223 patients support the anatomical integrity of cortical language areas and the origin of language
224 disturbances in CKD is still unknown.

225 Visuospatial abilities reflect the identification and localization of visual objects. It can be
226 tested, e.g., by asking someone to copy a complex figure (as in the Rey-Osterrieth Complex
227 Figure Test). Visuospatial performance is variably affected in CKD patients, depending on the
228 study^{56,58}, possibly because its impairment can be observed only in advanced CKD stages
229 and ESRF⁵. This is also supported by the absence of morphological alterations on MRI in the
230 occipital cortex of CKD patients, this being the region involved in visuospatial attention⁵⁹.

231 Finally, most of the literature supports the presence of “executive dysfunction” in CKD, with
232 an impairment in the Trail making tests (TMT-A and TMT-B), which addresses visual
233 attention and executive functions. These tests have been found to be consistently altered in
234 CKD patients in several studies. In a comparative study, the impairment in this cognitive
235 domain occurs with greater frequency in CKD compared with language, memory and
236 visuoconstructive abilities⁵⁶; it worsens over time in HD patients⁶⁰. It is also dependent on the
237 degree of kidney impairment, with a linear relation between both TMT-A and TMT-B scores
238 and eGFR⁶¹. Kidney transplant improves TMT-A scores when compared with patients on
239 HD⁶². As discussed above, the frontal lobe, which is the brain structure that is mainly
240 responsible for executive functions, is thinner in patients with CKD, possibly contributing to
241 this behavioral disorder. Notably, pediatric and adolescent patients with CKD already show
242 cognitive impairment in several domains⁶³, together with brain damage on MRI⁶⁴,
243 strengthening the concept that these changes are not solely due to the effect of ageing in
244 patients with CKD.

245 In summary, the cognitive impairment in CKD extends to several brain functional domains
246 and might be the result of damage to multiple cortical regions (particularly the frontal lobe),
247 and to subcortical modulatory neurons (particularly adrenergic neurons in the mesencephalon
248 and cholinergic neurons in Meynert's nucleus). In contrast, non-CKD dementia is
249 accompanied by structural MRI abnormalities of different brain regions: (i) in AD, at early
250 stage, the entorhinal cortex and cingulate, closely followed by the hippocampus, amygdala,
251 and parahippocampus; the atrophy then involves the temporal cortex and then other cortical
252 sites^{47,65}; (ii) in the Fronto-Temporal Dementia the frontal and temporal lobe are mostly
253 affected at MRI⁴⁶; (iii) in the Lewy Bodies Dementia the cingulate and superior temporal-

occipital cortex⁴⁷; (iv) in vascular dementia there is global cortical atrophy with involvement of white matter (so-called “white matter hyperintensities”); compared to AD the frontal cortex is more often involved, with lesions to association tracts by MRI⁶⁶.

3. Intermediate phenotypes: Neuroanatomical alterations, sleep disorders and tremor

In this section, we will use the term “intermediate phenotype” to describe a brain feature that lies between the complex behavioral trait (e.g., dementia) and a putative underlying molecular cause. Sometimes the terms “intermediate phenotype”, “biomarker” and “endophenotype” are used loosely and interchangeably⁶⁷. This brain feature, measurable and quantitative, is linked to simple neuronal networks and may be used as a proxy for the more complex behavior: such a feature is likely to have a linear relationship to the molecular changes accompanying CKD. Potential intermediate endophenotypes are the MRI brain correlates of dementia/MCI (discussed above) and quantitative phenotypes such as altered sleep pattern and motor control.

3. 1. Sleep

Sleep disorders can be quantified using polysomnography and actigraphy systems. Sleep disorders in CKD are very common with the majority of patients complaining of some form of sleep disorder⁶⁸. They include a reduction in total sleep time, insomnia/sleep fragmentation, daytime somnolence, altered circadian rhythm, sleep apnea or restless legs syndrome^{69,70}. Sleep apnea affects 34-56% of adult CKD patients^{71,72} and 56% of ESRF patients on HD^{73,74}. It is usually absent in pediatric patients with CKD⁷⁵. In 22-27% of adult CKD patients sleep apnea depends on a dysfunction of the neuronal drive (central sleep apnea, CSA)^{76,77}. The nocturnal hypoxemia that accompanies sleep apnea in CKD patients is associated with autonomic dysfunction and left ventricular hypertrophy^{78,79}, and predicts a high risk for cardiovascular events in ESRF⁷⁸. A meta-analysis concluded that sleep quality can be improved by renal replacement therapies (transplant, dialysis), even if it does not return to normal levels, and it does not depend on the intensity of therapy⁶⁹.

Sleep disorders are tightly linked to MCI and dementia⁸⁰. They are indicative of an existing brain damage. It is unclear if they induce further brain dysfunction, as pharmacological restoration of sleep does not improve cognitive functions⁸¹. In humans inadequate sleep has been associated with lower gray matter volume⁸². In animal models of CKD, serotonergic neurons in the dorsal raphe and histaminergic neurons in the hypothalamus (Figure 2), which are responsible for the maintenance of sleep patterns, show increased activity (indexed by cFos expression)⁴⁸. Serotonergic neurons influence the sleep-wake pattern and attention

memory and locomotor activity⁸³ and contribute to the depression and uremic anorexia seen in advanced CKD⁸⁴.

Overall, the sleep patterns and sleep apnea in CKD could be an easily quantifiable and ideal parameter linking the behavioral scale phenotype to the molecular scale (Figure 3).

291

3. 2 Motor control and tremor

Motor control and hand tremor can be easily quantified using force plates and accelerometers. CKD is accompanied by changes in balance and gait control⁸⁵. Specifically, patients with ESRF and MCI have a slower gait speed^{23,61} and reduced single-leg standing time (indexing balance function)²³ that is not due to a reduced muscle strength. The control of hand posture (resulting in small oscillations or physiological tremor) is also likely to be modified in advanced CKD: it has been known for a longtime that acute uremic intoxication or “uremic encephalopathy” is accompanied by hand tremor⁸⁶. The assumption that hand tremor is a result of uremic toxins derives from the observation that HD greatly improves tremor in cases of uremic encephalopathy⁸⁷. The altered motor control in CKD patients is also evident as a slower reaction time to visual or auditory stimuli^{88,89} and voice tremor⁹⁰.

The motor control modifications (postural instability, hand tremor, gait speed) in CKD are likely to be collateral features of cognitive impairment. Indeed, non-CKD cognitive impairment is accompanied (or preceded) by a slower gait speed⁹¹ and postural instability⁹². Furthermore, some forms of AD are accompanied by hand and postural tremor and limb bradykinesia⁹³.

As discussed above, norepinephrine and serotonin neurons modulate sleep and subcortical motor circuits (e.g., the basal ganglia and the spinal cord), possibly mediating the gait and hand instability in CKD. A pictorial review of the hierarchical organization from molecular abnormalities to a complex behavioral scale is represented in Figure 3.

312

4. Mechanisms of cognitive dysfunction in CKD

The link between CKD and cognitive dysfunction or its intermediate phenotype is not well understood. In pediatric populations, genetic factors may play a role, whereas in adult populations CKD-related vascular factors and uremic (neuro)toxins may have a greater impact. Every proposed mechanism should be examined in more detail, because of the potential for new therapeutic approaches, which are still limited.

4. 1 Genetic Factors

There has been little attention paid to the role of genetic factors in the relationship between CKD and cognitive function. However, a distinction must be made between pediatric and adult CKD. In the pediatric population kidney diseases may have a clear genetic determinant⁹⁴, for example, in up to 30% of steroid-resistant nephrotic syndrome patients⁹⁵. In these cases, neurocognitive impairment may derive from a genomic disorder that causes both CKD and cognitive impairment⁹⁶. Indeed, some rare genetic syndromes are well known to cause both cognitive impairment and kidney dysfunction, such as Bardet Biedl syndrome⁹⁷, Fabry disease⁹⁸, Schmike immunoosseus dysplasia⁹⁹, Joubert syndrome¹⁰⁰, tuberous sclerosis¹⁰¹ and oculocerebrorenal syndrome of Lowe¹⁰².

Conversely, in adult CKD a genetic diagnosis is found in only 10% of cases¹⁰³ and in pediatric steroid-sensitive CKD, almost no patient has a genetic diagnosis⁹⁵. In these cases a genetic predisposition to cognitive impairment has been suggested from the observation that genetic variants of α -Klotho, a CKD-dependent factor, affect cognition¹⁰⁴. Furthermore, circulating α -Klotho has been linked to cognitive decline¹⁰⁵. The analysis of genetic loci associated with adult CKD obtained from one million subjects, published in 2019, reports 147 loci relevant for kidney function¹⁰⁶. Among these, 13 polymorphisms had an Exonic effect (SLC47A1, EDEM3, SLC22A2, PPM1J, RPL3L, EPB41L5, TSPAN9, KLHDC7A, CPS1, C9, CACNA1S, SLC25A45, CERS2). Intriguingly, some of these genes are also expressed in the brain, particularly in the striatum (SLC47A1, KLHDC7A, SLC25A45; Allen Brain Atlas database), cortex (EDEM3, PPM1J, CERS2; Human Protein Atlas database), cerebellum and hippocampus (TSPAN9, EPB41L5; Human Protein Atlas database). Furthermore, some of these are related to diseases of the nervous system such as Infantile onset spinocerebellar ataxia (TSPAN9, CACNA1S, RPL3L; Rare Diseases AutoRIF ARCHS4 Predictions database) or AD (CACNA1S, WikiPathways database).

Finally, it is likely that any genetic predisposition to cognitive impairment in the general population is also operative in CKD. In fact, experimental data in rodent models suggest that the number of genes influencing memory and cognition is likely to be quite large¹⁰⁷.

Unfortunately, the quest for genetic risk factors in dementia and MCI using Genome-Wide Association Studies (GWAS) has only identified gene variants with a small effect size. The GA@ACE study comprised 4120 AD cases and 3289 controls, analyzing 7.7 million gene variants¹⁰⁸ and found only one already known marker with Genome Wide significance,

352 APOE- ϵ 4 rs429358. Other genetic variants had very small effects (such as CD33-rs3865444,
353 with OR=0.92). An additional genetic predisposition to MCI in CKD patients derives from
354 the genetic control of autoregulation of both renal and cerebral blood flow, which is discussed
355 further below.

356 When summing each small effects of all genetic variants in an individual, the “calculated
357 total risk score”, results are promising¹⁰⁹. For example, a genetic risk score based on eight
358 gene variants found a two-fold more rapid progression from MCI to AD when six or more
359 alleles were present¹¹⁰.

360 In summary, genetic risk for MCI/dementia in CKD is more easily recognized and important
361 in the pediatric population; in the adult population a genetic risk score from multiple variants
362 needs to be considered.

363

364 **4. 2 Non-genetic Factors**

365 Many different mechanisms have been proposed to link CKD and cognitive impairment. It
366 should be emphasized that the MCI/dementia link with CKD might actually represent one of
367 the very few established causes of cognitive impairment.

368 Most proposed mediators of brain damage are retained because of kidney dysfunction and
369 affect the brain through direct or indirect mechanisms. There are, however, notable
370 exceptions: (i) iatrogenic factors, namely dialysis, medications¹¹¹ and nutrition/diet; (ii)
371 comorbid conditions that cannot be easily separated from CKD such as hypertension and
372 cardiovascular disease; (iii) social factors and functional impairment (such as impairment in
373 using the telephone, preparing meals or shopping) that affect the psychological state of
374 patients with CKD.

375 Complex changes affect the blood composition of patients with CKD, which complicates
376 attempts to identify a unifying causative mechanism for CKD-MCI. Moreover, evaluation of
377 the mechanisms by which CKD-related changes in blood constituents might affect cognitive
378 function requires consideration of the time-scale over which cognitive decline occurs. Some
379 blood constituents (e.g., oxygen free radicals, volume status, electrolyte and acid-base
380 disturbances, and some uremic toxins and drugs) have effects within a short time-scale,
381 whereas others (e.g., amyloid deposits, inflammation, vascular dysfunction, nutrition, anemia)
382 require months or perhaps years to have an effect on the brain. Furthermore, the blood-brain
383 barrier (BBB) and blood-cerebrospinal fluid (BCB) barriers do not allow all blood

constituents to freely enter the brain parenchyma¹¹². The brain is likely to develop MCI/dementia over a relatively long time-scale (months to years)³⁹ and clearly MCI/dementia is a phenomenon that occurs at a higher scale of organization of neuronal networks or above.

In the section that follows, we briefly review the few attempts that have been made so far to interfere with MCI/dementia-CKD, before considering some possible underlying mechanisms in more detail.

391

4. 2. 1 Vascular dysfunction in CKD and cognitive decline

4. 2. 1. 1 Morphology of the brain vessels in CKD

CKD has a high prevalence of atherosclerosis and endothelial dysfunction is almost universal¹¹³. Vascular disease is associated with cognitive decline in non-CKD patients and is an important factor in CKD morbidity¹¹⁴. Brain capillaries and small vessels are not accessible in patients with CKD; hence, a useful proxy is the study of retinal capillaries, which can be quantified *in vivo*. In the retina, CKD stage 3 (or proteinuria >500mg/g creatinine) is accompanied by greater arteriolar wall-to-lumen ratio, greater wall thickness and greater inter-capillary distance¹¹⁵. Therefore, anatomical alterations in the brain macro- and micro-circulation are present in patients with CKD.

The endothelial dysfunction (indexed by sVCAM-1, thrombomodulin, sICAM-1 and sICAM-3) is a feature of CKD, HD and PD¹¹⁶, and is accompanied by an increased permeability of the blood brain barrier^{49,117}.

405

4. 2. 1. 2 Hemodynamic changes that occur in CKD

In non-CKD patients the vascular hypothesis of cognitive dysfunction is based on the hypothesis that anatomical vascular changes are accompanied by reduced cerebral blood flow, and consequent impairment in neuronal activities. Dysfunction of vascular pericytes in the brain, mediated by, for example, endothelin, has been shown to participate in the altered blood flow observed in dementia¹¹⁸.

As we shall see, patients with CKD show actually increased cerebral blood flow, which does not support the more general paradigm of vascular dysfunction.

414CKD is invariably accompanied by an increase in arterial blood pressure. Hypertension is a
415known risk factor for dementia in non-CKD patients¹¹⁹.

416Unexpectedly, in adult patients with CKD the global cerebral blood flow (measured by MRI
417arterial spin labeling) is increased compared with healthy controls. The increase was more
418evident in non-dialysis ESRF patients than in HD and PD patients. The changes did not
419correlate with neuropsychological tests when anemia was taken into account¹²⁰. These results
420were also confirmed in pediatric patients with CKD, who also showed an increase in global
421cerebral blood flow (measured by MRI arterial spin labeling) compared with healthy controls,
422though possibly due to a reduced hematocrit¹²¹. These findings lead to the counterintuitive
423interpretation that a decrease in cerebral blood flow may improve cognition in CKD¹²². It is
424plausible that the increased blood flow represents, in this case, a compensatory effect of
425anemia.

426These data and the lack of efficacy of anti-hypertensive drugs in MCI/dementia-CKD
427strongly suggest that the vascular hypothesis of dementia in the general population may not
428be correct or a complete explanation in CKD. However, it should be noted that patients with
429ESRF on HD have more complex, acute and variable hemodynamic changes triggered by the
430presence of an arterovenous (AV) fistula and the need for intermittent ultrafiltration.

431The AV fistula has a remarkable cardio-circulatory effect. Its effect on cognition compared
432with central venous catheter is unknown, although overall it is likely to be associated with a
433better quality of life for dialysis patients¹²³. However, intermittent ultrafiltration, which
434acutely reduces the blood volume, is also expected to reduce cardiac output and mean arterial
435pressure¹²⁴, which in turn reduces splanchnic and brain perfusion. Indeed, at the end of an HD
436session, cerebral blood flow is reduced, as demonstrated by [¹⁵O]H₂O PET-CT scan¹²⁵.

437Similarly, at the end of PD a reduced cerebral blood flow (measured by MRI arterial spin
438labeling) has been observed compared with pre-dialysis^{120,122}. However, in the interval
439between HD sessions (48h after the last dialysis session) a rebound effect has also been
440described, with an increase in the mean blood flow velocity (measured by Doppler
441ultrasound), partially related to changes in hemoglobin levels¹²⁶.

442Therefore, the blood flow changes in HD and PD are of short duration, but whether these
443chronic intermittent changes worsen cognition is unclear. However, the similar prevalence of
444MCI/dementia in advanced CKD, in HD and in PD suggests that the effect of dialysis
445treatment on brain hemodynamics is reversible and not additive in any way.

446

447 **4. 2. 1. 3. A genetic factor that causes impaired autoregulation**

448 Patients with CKD show on MRI focal white matter hyperintensities that are interpreted as
 449 small ischemic regions¹²⁷. This poses the problem of whether cognitive dysfunction in CKD
 450 is a form of “vascular dementia”, which has been studied widely in the general population.
 451 Unfortunately, a formal comparison between vascular dementia and CKD-dementia has never
 452 been carried out. An additional point of confusion is that vascular dementia is often linked to
 453 hypertension, which is a common finding in CKD.

454 Hypertension has usually been associated with small lacunar infarcts and diffuse areas of
 455 chronic ischemia (leukoaraiosis), chronic hypoperfusion and impaired cerebral autoregulation.
 456 It also has a genetic predisposition, associated with genes governing endothelial function,
 457 such as polymorphisms of angiotensin-converting enzyme, angiotensinogen, endothelin,
 458 eNOS, and methylenetetrahydrofolate reductase (MTHFR)¹²⁸. In rats, a genetic variant of the
 459 Add3 gene and a genetic deficiency of 20-HETE have been associated with impaired
 460 autoregulation of both renal and cerebral blood flow^{129,130}. Specifically, genetically
 461 hypertensive rats (Dahl salt-sensitive) show deficient formation of 20-HETE with an
 462 impaired myogenic response of cerebral arteries and blood-brain-barrier leakage¹³⁰.

463 As discussed above, in CKD cerebral blood flow is augmented, rather than decreased, which
 464 is opposite to what has been shown in vascular dementia. Thus, it is possible that a
 465 dysfunction of endothelial cells or glial cells modifies the exchange of substances between
 466 blood and neurons. Cerebral blood flow may be adequate or even increased, but the blood
 467 brain barrier or brain glymphatic system might be dysfunctional.

468

469 **4. 2. 1. 4 Brain glymphatic system**

470 The glymphatic or perivascular system is a CNS clearance system formed by astroglial cells -
 471 a cell species covering the whole cerebral vasculature - that efficiently eliminates soluble
 472 proteins and various metabolites from the CNS¹¹², and is responsible for ~60% of β -amyloid
 473 clearance¹³¹ (Figure 4). Vascular diseases, hypertension, diabetes, and neurodegenerative
 474 diseases may all reduce glymphatic clearance¹³². Moreover, neuroinflammation and
 475 depression have also been shown to suppress glymphatic clearance, perhaps explaining why
 476 these conditions increase the risk of developing dementia¹³². Interestingly, glymphatic
 477 clearing of waste products occurs primarily during sleep and in particular in stages 3-4

NREM sleep¹³³. Although it is not known how CKD affects the glymphatic system, the existing literature suggests that glymphatic fluid transport may be suppressed in CKD and that glymphatic dysfunction can lead to an accumulation of potential neurotoxic waste products. As discussed above, sleep disturbance is common in CKD patients⁶⁸ and accompanies the cognitive decline in MCI¹³⁴ and dementia¹³⁵. Furthermore, sleep apnea and AD are both linked to reduced level of Amyloid- β in cerebrospinal fluid, indicating that glymphatic clearance is suppressed in these conditions^{136,137}.

485

4. 2. 2 Uremic (neuro)toxins and kidney neurotrophins

The EUTOX database (<http://www.uremic-toxins.org/DataBase.html>) provides an updated list of all known uremic toxins and their characteristics. According to EUTOX, 9% of the known uremic toxins (7 over a total of 75 solutes) are associated with neurological and CNS effects. HD efficiently eliminates water-soluble toxins and improves acute uremic encephalopathy, but it is relatively ineffective when it comes to protein-bound or middle-sized toxins, and does not ameliorate chronic cognitive dysfunction in patients with ESRF (Table 1). The fact that this extracorporeal treatment does not improve cognitive dysfunction in ESRF implicates protein-bound and larger molecular weight toxins in MCI/dementia in these patients.

Many of the uremic bioproducts reported in Table 1 are known to exert a protective effect on neurons, but most of them do not cross the BBB under basal conditions (as reported in Table 1), and so cannot make contact with neurons *in vivo* and are unlikely to provide neuroprotection. Leakage of most of these products in uremia is currently untested, although it is known that the BBB is less functional in advanced CKD. Conversely, some uremic toxins easily cross the BBB under basal conditions and have detrimental effects on the endothelium and vasculature. NPY is of particular interest among uremic toxins. This 36-amino acid peptide has been implicated in neurodegenerative diseases such as AD¹³⁸. It is produced centrally (within the brain by specific neurons) and peripherally in nerve endings. Plasma NPY mostly derives from peripheral nerve endings, with an unclear correlation with the NPY coming from the cerebrospinal fluid¹³⁹. However, it has been reported to readily enter the brain from blood by diffusion across the BBB¹⁴⁰. Independent of BMI, serum NPY levels are elevated in CKD patients¹⁴¹ and in patients with sleep apnea; continuous airway positive pressure reduces NPY levels in these patients¹⁴². NPY levels predict a high risk for cardiovascular events both in CKD and in ESRF patients¹⁴³.

Because cognitive impairment is much more frequent in patients with cardiovascular disease, particularly in those with heart failure¹⁴⁴, NPY may be implicated in the pathogenesis of these alterations in CKD. In fact, high NPY levels in supratentorial cerebrospinal fluid, at least in the short term, are associated with cognitive impairment in patients with subarachnoid hemorrhage¹⁴⁵. Finally, NPY is also responsible for endothelial dysfunction¹⁴⁶, which makes this substance a good candidate for brain impairment in CKD.

CKD patients often present with disturbed calcium and phosphate metabolism, high PTH and FGF23 levels, and low α -klotho (see earlier) and calcitriol levels. PTH is listed among the uremic toxins, but the evidence that this hormone is directly implicated in cognitive impairment is uncertain¹⁴⁷. PTH is a polypeptide of 84 amino acids, which is unlikely to cross the BBB under normal conditions. Furthermore, the level of expression of the PTH receptor in the brain is fairly low according to the Allen Brain Atlas. However, disturbed mineral metabolism may have an impact on cognitive impairment in CKD patients through pathways independent of PTH. The liver/bone/kidney isoform of alkaline phosphatase, an enzyme key to bone metabolism, is also expressed in neurons of the cerebral cortex (data from The Human Protein Atlas database: <https://www.proteinatlas.org/>). PTH is elevated in patients with AD and correlates inversely with cognitive function in these patients¹⁴⁸.

Experimental evidence suggests that high alkaline phosphatase, by dephosphorylating the tau-protein, a protein considered central to the pathogenesis of AD, may promote the binding of the same protein to muscarinic receptors (M1 and M3) in the hippocampal area, thereby triggering a marked increase in intracellular calcium levels and triggering cell death¹⁴⁹.

The phosphaturic hormone FGF23 increases early during the course of CKD and has been associated with cardiovascular disease and cardiovascular mortality¹⁵⁰. Moreover, in the Framingham study, higher FGF23 levels are associated with a higher risk for dementia¹⁵¹. α -klotho, the obligatory co-ligand of FGF23 is highly expressed in brain after the kidney and parathyroid glands¹⁵². Circulating α -klotho, as well as kidney and parathyroid α -klotho, are downregulated in CKD, but whether brain α -klotho is also affected is unknown. A recent MRI-based study found that reduced circulating α -klotho associated positively with the risk for dementia and cerebral deep white matter lesions, even after correction for reduced kidney function and other risk factors¹⁵³. Several genetic variants altering α -klotho protein levels are associated with β -amyloid burden and risk for dementia^{104,105,154}. Experimental evidence links α -klotho with the function of serotonergic neurons, hippocampal function, depression and dementia-like symptoms in animals¹¹⁵. While low α -klotho or high FGF23 appear to

544 exert negative effects on brain function, α -klotho or FGF23 deficiency also impair neuronal
545 processes, particularly in the hippocampus and possibly also cerebellum, affecting memory,
546 behavior, and motor functions^{155,156}. A common denominator of α -klotho or FGF23
547 deficiency is high calcitriol and reducing calcitriol levels to normal reverses or prevents brain
548 alterations in experimental animal models¹⁵⁷. In contrast, patients with CKD often suffer
549 from low calcitriol levels. This apparent contradiction that both high and low calcitriol levels
550 are linked to impaired brain functions may indicate an optimal range of calcitriol levels
551 necessary for neuroprotection, microglial immune function, and vascular integrity^{158,159}. At
552 present there is no evidence supporting calcitriol supplementation to delay loss of
553 psychomotor functions in elderly populations with CKD¹⁶⁰ (Figure 5).

554

555 **4. 4 Role of brain stem cells and neuroinflammation in CKD-dependent cognitive** 556 **impairment**

557 CKD is a pro-inflammatory dysmetabolic state with associated brain dysfunction.
558 Surprisingly little attention has been paid to the role of neural stem cells (or neural
559 precursor cells, NPCs) in CKD patients, given that NPCs play a key role in several
560 homeostatic brain functions and are extremely sensitive to their micro-environment. While
561 NPCs located within the sub-granular (SGZ) zones contribute via neurogenesis to
562 maintaining memory circuitry, behavior and spatial learning (e.g., endogenous NPCs produce
563 a constant albeit slow increase in hippocampal volume, which is needed for cognitive
564 functions and mood)^{161,162}, NPCs residing in the subventricular (SVZ) exert little or no
565 neurogenic functions, but contribute to counteracting metabolic dysfunction and/or
566 inflammatory processes), the so-called ‘bystander (or paracrine) effect’¹⁶³. This is due to the
567 ability of undifferentiated NPCs to secrete a milieu of homeostatic and/or neuroprotective
568 molecules (e.g., stem cell regulators, trophic factors and immunomodulators) that are thought
569 to be important, because, depending on the tissue microenvironment, they may stimulate
570 endogenous precursors to promote re-myelination or rescue (directly and indirectly) of
571 damaged axons and neurons^{162–164}. As a consequence, an additional pathogenic mechanism
572 that might contribute to irreversible glial and/or neuronal loss, and the neuronal functional
573 impairment underlying cognitive dysfunction in CKD patients, could be the effect of uremic
574 toxins, inflammatory cytokines (e.g., IL-1 β , IL-18, IL-6, TNF α), as well as anti-inflammatory
575 cytokines (e.g., IL-10) and free-radicals (Figure 4).

Among the inflammatory cytokines, IL-6 is increased 5-fold in HD patients, and permanently perturbs NPC proliferation and neurogenesis¹⁶⁵. IL-10, which is increased in HD, maintains NPCs in an undifferentiated proliferation state, rather than promoting differentiation¹⁶⁶. Both TNF α and IL-1 β also increase in HD and can stimulate NPC proliferative capacity¹⁶⁷. At present it is not clear if the differential effects of IL-10 and IL-1 β on NPCs have also different cognitive effects. Free radicals, which are increased in HD and CKD patients may strongly and negatively impact NPC function¹⁶⁸. Finally, cell-mediated innate immunity, thought to be involved in toxic uremia as a potential pathogenic mechanism causing cognitive impairment in CKD patients, might also be impaired when NPC homeostasis is disturbed¹⁶⁹. In kidney transplant patients cyclosporin and mycophenolate have direct inhibitory effects on NPCs¹⁷⁰, unlike everolimus¹⁷¹.

NPCs also play a role in neurodegenerative diseases such as AD: the deletion of genes necessary for NPCs and neurogenesis (such as Tet1, 5hmC) lead to learning and memory deficits in animal models^{172,173}.

It is becoming clear that uremic (neuro)toxins in CKD not only exert a detrimental effect on neural cells, but also on NPCs, although this is still not yet widely appreciated. Given the pleiotropic actions (homeostatic and reparative) of NPCs, and the accumulating evidence showing that during CKD circulating uremic toxins (whose CNS trafficking is facilitated by BBB damage) may impair CNS structure and function, this seems to be a new research avenue and opportunity in MCI-CKD worth pursuing.

5. Interventional studies

Interventional studies are essential for the identification of mechanistic links between kidney disease and brain alterations. At present most of the attempts to improve, prevent or delay MCI/dementia in CKD have been unsuccessful. We will review some of these attempts to make the reader aware of what has been already done. However, new drugs are now available to relieve some of the symptoms of dementia, relatively new dialysis regimens are being used today, and new anti-inflammatory therapies have been introduced for atherosclerosis and stroke: we list these approaches, which may yet prove beneficial.

HD is life-saving in patients with ESRF and reverses acute encephalopathy. The acute uremic encephalopathy or uremic delirium presents with impaired memory and attention, altered consciousness and disorganized thinking in untreated patients with ESRF. Today it is a rare

clinical presentation, because patients with ESRF usually undergo planned dialysis before this neurological syndrome can develop. When it does occur, neurological recovery may take days after dialysis initiation and in at least one case report a patient remained comatose for 5 days after correction of uremia¹⁷⁴. This supports the notion that circulating and brain-permeable small molecules, which are removed by dialysis, are likely to be responsible for acute uremic encephalopathy. In contrast, MCI and dementia develop over longer time-scales and reversibility is potentially possible only for MCI, rather established dementia.

However, the question is whether the clearance of blood toxins by HD can decrease the risk of developing MCI-CKD. Unfortunately, the partial correction of blood composition with HD seems unlikely to prevent or slow down MCI-dementia progression, which is suggested by a similar prevalence of MCI/dementia among patients on HD compared with those with advanced CKD who are not yet on dialysis¹⁷⁵. This inability of HD to attenuate MCI might be due to a suboptimal and discontinuous treatment regimen (with a rapid increase in toxin levels between dialysis sessions); however, more intensive dialysis regimens with improved dialysis adequacy (Kt/V) also do not improve MCI-related outcomes¹⁷⁶. Therefore, it is possible that some uremic (neuro)toxins, for example, medium-large size toxins and protein-bound toxins (listed in Table 1) are not adequately removed by HD. Unfortunately, no data are available on the effect of hemodiafiltration (HDF), which can potentially remove larger size toxins, on cognitive function. A meta-analysis suggests that PD treatment may be more advantageous than HD^{45,175}. However, there is inconsistency among studies, possibly because the effect is very small. In a large study enrolling 52'332 HD patients and 3'292 PD patients, the higher risk for cognitive impairment in HD disappeared after controlling for demographic characteristics and competing risks of death¹⁷⁷.

Therefore, the slower dynamics of ultrafiltration/dialysis of the peritoneal system or better removal of protein-bound toxins do not seem to lead to greater clinical improvement. Similarly, kidney transplantation attenuates MCI, but does not lead to the recovery of cognitive function to the levels of a control healthy population (see Figure 1)^{178,179}. This suggests that MCI-CKD is not easily reversible or that the immunosuppressive drugs used to avoid rejection also impinge on cognitive function.

Neuropsychological approaches are unlikely to improve MCI, because they do not remove the organic substrates causing the problem, nor are interventions (alone) that aim at better control of blood pressure or prevent cerebrovascular accidents (stroke and myocardial

640infarction)¹⁸⁰. This suggests that the vascular alterations observed in CKD are not the main
641cause MCI or that they do not respond to standard preventive strategies.

642Few interventional studies are available examining the diet/nutritional changes in CKD-MCI
643progression. Vitamin B and folate supplementation to reduce homocysteine did not result in a
644reduction in MCI-CKD¹⁸¹. L-carnitine improves cognitive function in a rat model of CKD,
645but no data are available in humans¹⁸². Vitamin D 25(OH)₂ levels can be low in CKD and
646hypo-vitaminosis D is associated with cognitive decline; however, no data are available on its
647supplementation to prevent MCI in CKD (see earlier).

648Antioxidants such as Vitamin E have been proposed to reduce brain oxidative stress and slow
649cognitive impairment in the general population, although with minimal effects in AD¹⁸³.
650Tempol, an antioxidant, has been tested in animal models of CKD with some neuroprotective
651effect¹⁸⁴.

652Unsaturated fatty acids such as omega-3, Mediterranean diet, and malnutrition are other
653dietary factors and nutritional aspects considered relevant in the general population, but with
654minimal effects on cognitive protection^{185,186}. No information on MCI-CKD is currently
655available with these approaches.

656Iron deficiency is also common in CKD and anemia is a risk factor for poor scores at
657neuropsychological tests. Unfortunately, no information is available on iron supplementation
658in CKD to prevent MCI. However, erythropoietin appears beneficial for cognitive
659dysfunction in CKD^{187,188}, which supports the role of CKD-dependent anemia in poor
660cognitive function. The recent introduction of hypoxia inducible factor (HIF) stabilizers as an
661oral alternative to injectable erythropoietin for anemia in CKD patients¹⁶⁹ awaits further
662assessment for its effect on MCI-CKD.

663The hypothesis of altered PTH/phosphate homeostasis in MCI-CKD has not been tested. At
664present there is only a single case report of the reversal of cognitive impairment after
665cinacalcet treatment¹⁸⁹.

666The neuroinflammatory hypothesis might have an additional support after the attempt to
667reduce atherosclerosis/endothelial dysfunction by targeting a postulated inflammatory
668mechanism. Canakinumab, an anti-interleukin-1 β antibody¹⁹⁰, and colchicine¹⁹¹ both
669reduced the effects of atherosclerosis and showed some effect on brain function. Specifically,
670Canakinumab reduced infarct size, cerebral oedema and improved neurological performance
671in an animal model of stroke¹⁹². Conversely, colchicine is neurotoxic when injected into the

672 brain¹⁹³, but if delivered in the bloodstream has anti-neuroinflammatory action potentially
673 useful for AD¹⁹⁴. Consistently, a trial on 4754 patients assigned to receive colchicine or
674 placebo showed neuroprotective effect of colchicine, with lower risk of stroke¹⁹¹.

675 This may support the hypothesis linking MCI-CKD to wider endothelial dysfunction.

676

677 **6. Conclusions**

678 Nephrologists need to be more aware of cognitive impairment in CKD. However, a major
679 problem is the lack of any mechanistic understanding and the paucity of data, and therefore
680 for any interventional strategies. More systematic and standardized neurophysiological
681 testing of CKD patients recruited to the increasing number of large prospective CKD cohorts
682 will help in defining more reliably the true extent of the problem of MCI-CKD and the
683 biomarkers linked to it. Hemodiafiltration or other high permeability membranes await
684 testing of their effect on cognition. Memantine, and acetylcholinesterase inhibitors (e.g.,
685 donepezil) that are used in dementia have an unclear role in CKD patients. Strategies to
686 improve endothelial and glymphatic function, and neuronal stem cell production in CKD are
687 still in their infancy. However, if any of these approaches can prove useful in MCI-CKD, this
688 could also be a significant step forward in treating dementia itself.

689

690

691 **BOX 1: MCI**

692 **Mild cognitive impairment (MCI):** a term used to identify subjects at risk to develop
693 dementia, but whose cognitive deficit is so mild that it does not impinge upon daily activities.
694 The diagnosis is based on symptoms reported/observed by patients, caregivers, informants
695 and clinicians. The symptoms include memory impairment, language difficulties, attention
696 deficit, disorientation and altered visuospatial skills. MCI is only a risk state: 90-95% of
697 subjects with MCI actually do not progress to dementia. However, while dementia is
698 irreversible, 14-44% of MCI subjects can recover to normal cognitive function. After the
699 introduction of the Diagnostic and Statistical Manual of Mental Disorders version 5 (DSM-5),
700 dementia has been renamed as major Neurocognitive disorder (major NCD) and MCI as mild
701 NCD. Correspondingly, the criteria for MCI have changed. The Petersen's criteria for MCI
702 are: (a) subjective decline in memory (b) memory impairment on neuropsychological test (c)
703 intact daily functioning (d) no dementia. The DSM-5 criteria for MCI are: (a) concern (of the

704 patient or of the clinician) of a mild decline in cognitive function (b) cognitive decline by
705 standard cognitive assessment (c) independence in everyday activities (d) cognitive deficits
706 not explainable by delirium, psychosis, severe depression.

707

708

709 **BOX 2: glossary**

710 **Attention:** the cognitive domain involved in the selection of a specific information
711 within a sensory channel (filtering), ignoring all the other data. It requires the activity of the
712 prefrontal cortex, with modulation by the dopaminergic system

713 **Inhibitory control:** the ability to suppress ongoing and inappropriate responses to
714 potentially relevant stimuli. A classical test is the Stroop task, requiring to name the font color
715 of a printed word, neglecting the meaning of the word itself.

716 **Memory:** the cognitive domain involved in the registration and recall of information.
717 Different and independent types of memory exist, such as explicit memory (for words,
718 history etc), implicit memory (for actions, skills), short term and working memory (with
719 limited number of items that can be recorded and short permanence) and long-term memory.
720 Although no single brain region can be linked to memory, at the neuronal scale the
721 phenomenon most likely correlated to memory is called “long term potentiation” and “long
722 term depression”, which are sustained modifications of the efficiency of the neuronal contacts
723 or synapses.

724 **Language skills:** the cognitive domain dealing with repeating, understanding and
725 producing words, sentences, language. They require the function of two main areas in the
726 dominant (left) cortex, that is the motor- and sensitive- language areas (Broca’s and
727 Wernicke’s areas)

728 **Visuospatial ability:** the cognitive domain dealing with the analysis of visual
729 information, recognition of images and reproducing drawings. It requires the integrity of the
730 occipital cortex.

731 **Executive functions:** a psychological construct indicating mental processes
732 necessary for goal-directed behavior. The term derives from subjects with damage of the
733 frontal lobe, who can show normal language, learning, memory and reasoning on specific
734 tasks; notwithstanding, their everyday tasks are disorganized and poorly planned: their
735 “cognitive resources” such as learning, memory, reasoning, language are poorly coordinated,

736 that is they exhibit an “executive dysfunction”. No direct access to executive functions is
737 possible, therefore they comprise many different psychological terms such as attention and of
738 inhibition, working memory, cognitive flexibility, planning, fluid intelligence, reasoning and
739 problem solving etc. It requires the integrity of the frontal lobe and its modulation by
740 dopamine and cholinergic neurons from the mesencephalon and basal forebrain respectively.

741 **Catecholamine neurons:** a small group of neurons (less than one million) mainly
742 localized in the encephalic trunk and comprising adrenergic/noradrenergic and dopaminergic
743 neurons. These neurons innervate large parts of the brain through a massive arborization of
744 their axons. They can subserve both simple computational task (such as indicating the
745 presence or absence of a reward) and tonic activity on target regions, such as the striatum and
746 the cortex, thereby controlling wakefulness and attention.

747 **Polysomnography.** An overnight sleep study based on neurophysiologic parameters
748 (EEG, electrooculography, electro-myography), respiratory patterns, pulse oxymetry, heart
749 rate. In clinical practice it is used, for example, for the diagnosis of Sleep Apnea and the
750 characterization of sleep disturbances.

751 **Actigraphy.** Usually a portable device (e.g. in the form of a bracelet) equipped with
752 motion sensors (accelerometers, gyroscopes, GPS), aimed at recording and characterizing the
753 motor activity and posture of a subject during the day or over several days. Step-meters are a
754 cheap and simple type of actigraphic recordings. Since sleep is accompanied by specific
755 postures (usually supine position) and immobility, actigraphic recordings can be used as a
756 first approach to study 24h sleep patterns in large populations, being inexpensive and
757 comfortable to wear (as opposed to polysomnography).

758 **Sleep apnea.** This is a common respiratory problem characterized by recurrent
759 episodes of apnea/hypopnea (no or reduced airflow) during sleep. The apneic episodes can
760 originate from a dysfunction of the brain respiratory centers (central sleep apnea) or from
761 alteration of the upper airways (e.g., pharynx and larynx) or the tone of their muscles
762 (peripheral sleep apnea).

763 **Dysautonomia.** Altered function of the autonomic nervous system (sympathetic and
764 parasympathetic) with consequent maladaptive control of orthostatic blood pressure,
765 digestion, and bladder emptying.

766 **Force plates.** A device to study where the body weight is released onto the floor over
767 time, and its magnitude. The position of the sum of all forces acting between the body and the

768 floor can be measured by force plates and is called Center of Pressure. The position of the
769 Center of Pressure changes over time during movements (such as walking) or even during
770 simple stance.

771 **Accelerometers.** Devices measuring the acceleration of an object over time. These
772 sensors are usually very small and can be applied onto the hand to measure hand tremor.
773 Even the widely available smartphones or game controllers may serve for this purpose.

774 **Blood-brain barrier (BBB) and blood-cerebrospinal fluid (BCB) barrier.** The
775 phenomenon by which many substances (such as India ink) and drugs injected into the blood
776 remain within the cerebral capillary bed without entering into the parenchyma (BBB) or the
777 cerebrospinal fluid (BCB). The anatomical substrate for this phenomenon is thought to
778 involve the peculiar structure of the brain capillary endothelium and the presence of a
779 pericapillary glial sheet.

780 **NREM sleep.** Using EEG it is possible to appreciate the oscillatory dynamics of
781 sleep, which is composed of 4-5 cycles of a long period without eye movements (non-rapid-
782 eye movements: NREM) followed by short rapid eye movement stage (REM). The NREM
783 state is further composed of progressive EEG alterations which can be classified in 4 stages.

784

Table 1. List of uremic neurotoxins uncleared or insufficiently cleared by dialysis and current therapeutic regimens. The impact on the brain is analyzed on cellular/tissue scale, intermediate phenotype scale and behavioral scale. BBB+: the toxin crosses the blood brain barrier; BBB-: the toxin does not cross the BBB (predicted from https://www.cbligand.org/BBB/). NA: data not available				
Name	Impact on the CNS			Solubility-protein bound; BBB crossing
	Microscopic scale (Cells/tissue)	Intermediate phenotypes	Behavioral scale	
Asymmetric Dimethyl Arginine (ADMA)	Endothelial dysfunction ²¹⁰	Vascular brain injury ²¹⁷ , slower gait speed ²¹⁸	Cognitive impairment	Water-soluble BBB-
beta-2-microglobulin	NA	NA	NA	Middle BBB-
3-Carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF)	Inhibition of brain-to-blood transport of metabolites ²¹¹	Sleep ²¹⁹		Protein-bound BBB+
Cystatin C	NA	Glymphatic solute clearance ²²⁰	NA	Middle BBB-
FGF23	Endothelial	NA	Memory	Middle

	dysfunction ²¹²		deficits ¹⁵¹	BBB-
Hippuric acid	Endothelial dysfunction ²¹³	BBB dysfunction	Uremic encephalopathy	Water-soluble BBB+
IL-1 beta	Neurodegeneration of dopamine neurons ¹⁹⁵	NA	Executive function, memory	Protein-bound BBB-
IL-6, TNF-alpha	Neuroinflammation ¹⁹⁶	Reduced glymphatic drainage ²¹⁴	NA	Middle BBB-
Indole-3-acetic acid	Effect on neuronal stem cells ¹⁹⁷	NA	NA	Protein-bound BBB+
Indoxylsulphate/p-cresylsulphate	Neuroinflammation and altered glial function ¹⁹⁸	NA	Cognitive impairment ²²¹	Protein-bound BBB+
Leptin	Neuroprotective; apoptosis in neural stem cells ; adiposity-dependent neurotoxicity ^{199,200}	NA	NA	Protein-bound BBB-
Methylglyoxal	Effects on neural stem cells, Amyloid deposition ^{201,202}	Lower gray matter	Memory, executive functions ²⁰²	Protein-bound BBB+
Neuropeptide Y	Endothelial	Sleep	NA	Middle

(NPY)	dysfunction ¹⁴⁶	regulation		BBB+
Parathyroid hormone (PTH)	NA	Gait instability ²¹⁵	NA	Middle BBB-
Spermidine/putrescine	NA	NA	NA	Protein-bound BBB-
Putative kidney neurotrophins				
Erythropoietin	Increases brain aquaporin 4 (glymphatic pathway) ²⁰³	Neuronal oxygenation	Improves behavioral deficit	Middle BBB-
Hydrogen sulfide (H2S)	Promotes neuronal stem cell differentiation; Neuroprotective effects ^{204,205}	NA	Improves behavioral deficit	Water-soluble BBB+
Uric acid	Protective on dopamine system; Promotes neuronal stem cell differentiation ^{206,207}	Increases brain perivascular spaces (glymphatic pathway) ²¹⁶	NA	Water-soluble BBB+
Vitamin D-calcitriol	Decreases neuroinflammation; promotes neurogenesis ^{208,209}	NA	Maintains global cognitive performance ²²²	Protein-bound BBB+

786

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789

790 **Conflicts of interest**

791 All authors report no conflict of interest

792

793

References

1. American Psychiatric Association. *DSM-5: diagnostic and statistical manual of mental disorders*. (American Psychiatric Publishing, 2013).
2. Marcos, G. *et al.* Conversion to dementia in mild cognitive impairment diagnosed with DSM-5 criteria and with Petersen's criteria. *Acta Psychiatr. Scand.* **133**, 378–385 (2016).
3. Viggiano, D. *et al.* Mild cognitive impairment and kidney disease: clinical aspects. *Nephrol. Dial. Transplant* (2019). doi:10.1093/ndt/gfz051
4. Lipnicki, D. M. *et al.* Risk Factors for Mild Cognitive Impairment, Dementia and Mortality: The Sydney Memory and Ageing Study. *J. Am. Med. Dir. Assoc.* **18**, 388–395 (2017).
5. Brodski, J., Rossell, S. L., Castle, D. J. & Tan, E. J. A Systematic Review of Cognitive Impairments Associated With Kidney Failure in Adults Before Natural Age-Related Changes. *J. Int. Neuropsychol. Soc.* **25**, 101–114 (2019).
6. Ekblad, L. L. *et al.* Albuminuria and Microalbuminuria as Predictors of Cognitive Performance in a General Population: An 11-Year Follow-Up Study. *J. Alzheimers. Dis.* **65**, 1053–1054 (2018).
7. Martens, R. J. H. *et al.* Estimated GFR, Albuminuria, and Cognitive Performance: The Maastricht Study. *Am. J. Kidney Dis.* **69**, 179–191 (2017).
8. Joosten, H. *et al.* Association of cognitive function with albuminuria and eGFR in the general population. *Clin. J. Am. Soc. Nephrol.* **6**, 1400–9 (2011).
9. Weiner, D. E. *et al.* Cognitive Function and Kidney Disease: Baseline Data From the Systolic Blood Pressure Intervention Trial (SPRINT). *Am. J. Kidney Dis.* **70**, 357–367 (2017).
10. Berger, I. *et al.* Cognition in chronic kidney disease: A systematic review and meta-analysis. *BMC Med.* **14**, 1–10 (2016).
11. Sacre, J. W. *et al.* Associations of Chronic Kidney Disease Markers with Cognitive Function: A 12-Year Follow-Up Study. *J. Alzheimer's Dis.* **70**, 1–12 (2018).
12. O'Lone, E. *et al.* Cognition in people with end-stage kidney disease treated with hemodialysis: A systematic review and meta-analysis. *Am. J. Kidney Dis.* **67**, 925–935 (2016).
13. Harhay, M. N. *et al.* Cognitive Impairment in Non-Dialysis-Dependent CKD and the Transition to Dialysis: Findings From the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am. J. Kidney Dis.* **72**, 499–508 (2018).
14. Chu, N. M. *et al.* Frailty and Changes in Cognitive Function after Kidney Transplantation. *J. Am. Soc. Nephrol.* ASN.2018070726 (2019). doi:10.1681/ASN.2018070726
15. Drew, D. A., Weiner, D. E. & Sarnak, M. J. Cognitive Impairment in CKD: Pathophysiology, Management, and Prevention. *Am. J. Kidney Dis.* **74**, 782–790 (2019).

82916. Zammit, A. R., Katz, M. J., Bitzer, M. & Lipton, R. B. Cognitive Impairment and Dementia in
830 Older Adults With Chronic Kidney Disease: A Review. *Alzheimer Dis. Assoc. Disord.* **30**, 357–
831 366
83217. Chillon, J.-M., Massy, Z. A. & Stengel, B. Neurological complications in chronic kidney
833 disease patients. *Nephrol. Dial. Transplant* **31**, 1606–14 (2016).
83418. Kurella Tamura, M. *et al.* Vascular risk factors and cognitive impairment in chronic kidney
835 disease: the Chronic Renal Insufficiency Cohort (CRIC) study. *Clin. J. Am. Soc. Nephrol.* **6**,
836 248–56 (2011).
83719. Kelly, D. & Rothwell, P. M. Disentangling the multiple links between renal dysfunction and
838 cerebrovascular disease. *J. Neurol. Neurosurg. Psychiatry* 1–10 (2019). doi:10.1136/jnnp-
839 2019-320526
84020. Lu, R., Kiernan, M. C., Murray, A., Rosner, M. H. & Ronco, C. Kidney-brain crosstalk in the
841 acute and chronic setting. *Nature Reviews Nephrology* **11**, 707–719 (2015).
84221. Simões E Silva, A. C., Miranda, A. S., Rocha, N. P. & Teixeira, A. L. Neuropsychiatric
843 Disorders in Chronic Kidney Disease. *Front. Pharmacol.* **10**, 932 (2019).
84422. Burns, C. M. *et al.* Prevalence and Risk of Severe Cognitive Impairment in Advanced Chronic
845 Kidney Disease. *Journals Gerontol. - Ser. A Biol. Sci. Med. Sci.* **73**, 393–399 (2018).
84623. Orobe, Y. *et al.* Mild cognitive impairment in older adults with pre-dialysis patients with
847 chronic kidney disease: Prevalence and association with physical function. *Nephrology*
848 (*Carlton*). **24**, 50–55 (2019).
84924. Hobson, P., Lewis, A., Nair, H., Wong, S. & Kumwenda, M. How common are neurocognitive
850 disorders in patients with chronic kidney disease and diabetes? Results from a cross-sectional
851 study in a community cohort of patients in North Wales, UK. *BMJ Open* **8**, e023520 (2018).
85225. Kalirao, P. *et al.* Cognitive impairment in peritoneal dialysis patients. *Am. J. Kidney Dis.* **57**,
853 612–620 (2011).
85426. Manly, J. J. *et al.* Frequency and course of mild cognitive impairment in a multiethnic
855 community. *Ann. Neurol.* **63**, 494–506 (2008).
85627. McAdams-Demarco, M. A. *et al.* Frailty and cognitive function in incident hemodialysis
857 patients. *Clin. J. Am. Soc. Nephrol.* **10**, 2181–2189 (2015).
85828. Fukunishi, I. *et al.* Psychiatric disorders among patients undergoing hemodialysis therapy.
859 *Nephron* **91**, 344–347 (2002).
86029. US Renal Data System, A. USRDS 2005 Annual Data Report: Atlas of End-Stage Renal
861 Disease in the United States. *Bethesda, MD Natl. Institutes Heal. Natl. Inst. Diabetes Dig.*
862 *Kidney Dis.* 140–143 (2005).
86330. McAdams-DeMarco, M. A. *et al.* Dementia, Alzheimer’s Disease, and Mortality after
864 Hemodialysis Initiation. *Clin. J. Am. Soc. Nephrol.* **13**, 1339–1347 (2018).
86531. Ponjoan, A. *et al.* Epidemiology of dementia: prevalence and incidence estimates using
866 validated electronic health records from primary care. *Clin. Epidemiol.* **11**, 217–228 (2019).

86732. McAdams-DeMarco, M. A. *et al.* Dementia and Alzheimer's Disease among Older Kidney
868 Transplant Recipients. *J. Am. Soc. Nephrol.* **28**, 1575–1583 (2017).
86933. van der Flier, W. M. & Scheltens, P. Epidemiology and risk factors of dementia. *J. Neurol.*
870 *Neurosurg. Psychiatry* **76 Suppl 5**, v2-7 (2005).
87134. Kurella Tamura, M. & Yaffe, K. Dementia and cognitive impairment in ESRD: diagnostic and
872 therapeutic strategies. *Kidney Int.* **79**, 14–22 (2011).
87335. Kuo, Y.-T. *et al.* Risk of dementia in patients with end-stage renal disease under maintenance
874 dialysis-a nationwide population-based study with consideration of competing risk of mortality.
875 *Alzheimers. Res. Ther.* **11**, 31 (2019).
87636. Lizio, R. *et al.* Different abnormalities of cortical neural synchronization mechanisms in
877 patients with mild cognitive impairment due to Alzheimer's and chronic kidney diseases: An
878 EEG study. *J. Alzheimer's Dis.* **65**, 897–915 (2018).
87937. Albert, M. S. *et al.* The diagnosis of mild cognitive impairment due to Alzheimer's disease:
880 recommendations from the National Institute on Aging-Alzheimer's Association workgroups
881 on diagnostic guidelines for Alzheimer's disease. *Alzheimers. Dement.* **7**, 270–9 (2011).
88238. Jellinger, K. A. Should the word 'dementia' be forgotten? *J. Cell. Mol. Med.* **14**, 2415–6 (2010).
88339. Mendley, S. R. *et al.* Duration of chronic kidney disease reduces attention and executive
884 function in pediatric patients. *Kidney Int.* **87**, 800–6 (2015).
88540. Madan, P., Kalra, O. P., Agarwal, S. & Tandon, O. P. Cognitive impairment in chronic kidney
886 disease. *Nephrol. Dial. Transplant* **22**, 440–4 (2007).
88741. Singh, N. P. *et al.* Effect of improvement in anemia on electroneurophysiological markers
888 (P300) of cognitive dysfunction in chronic kidney disease. *Hemodial. Int.* **10**, 267–73 (2006).
88942. Sharma, A. *et al.* Impact of Cognitive Function Change on Mortality in Renal Transplant and
890 End-Stage Renal Disease Patients. *Am. J. Nephrol.* **44**, 462–472 (2016).
89143. Qiu, Y. *et al.* Structural and functional brain alterations in end stage renal disease patients on
892 routine hemodialysis: a voxel-based morphometry and resting state functional connectivity
893 study. *PLoS One* **9**, e98346 (2014).
89444. Song, S. H., Kim, I. J., Kim, S.-J., Kwak, I. S. & Kim, Y.-K. Cerebral glucose metabolism
895 abnormalities in patients with major depressive symptoms in pre-dialytic chronic kidney
896 disease: statistical parametric mapping analysis of F-18-FDG PET, a preliminary study.
897 *Psychiatry Clin. Neurosci.* **62**, 554–61 (2008).
89845. Tian, X. *et al.* The comparison of cognitive function and risk of dementia in CKD patients
899 under peritoneal dialysis and hemodialysis: A PRISMA-compliant systematic review and
900 meta-analysis. *Medicine (Baltimore).* **98**, e14390 (2019).
90146. Boccardi, M. *et al.* The MRI pattern of frontal and temporal brain atrophy in fronto-temporal
902 dementia. *Neurobiol. Aging* **24**, 95–103 (2003).
90347. Blamire, A. M. MR approaches in neurodegenerative disorders. *Prog. Nucl. Magn. Reson.*
904 *Spectrosc.* **108**, 1–16 (2018).

90548. Palkovits, M. *et al.* Neuronal activation in the central nervous system of rats in the initial stage
906 of chronic kidney disease-modulatory effects of losartan and moxonidine. *PLoS One* **8**, e66543
907 (2013).
90849. Mazumder, M. K., Paul, R., Bhattacharya, P. & Borah, A. Neurological sequel of chronic
909 kidney disease: From diminished Acetylcholinesterase activity to mitochondrial dysfunctions,
910 oxidative stress and inflammation in mice brain. *Sci. Rep.* **9**, 3097 (2019).
91150. Deng, G., Vaziri, N. D., Jabbari, B., Ni, Z. & Yan, X. X. Increased tyrosine nitration of the
912 brain in chronic renal insufficiency: reversal by antioxidant therapy and angiotensin-
913 converting enzyme inhibition. *J. Am. Soc. Nephrol.* **12**, 1892–9 (2001).
91451. Jones, D. J. W. *et al.* The nature of impairments of memory in patients with end-stage renal
915 disease (ESRD). *Physiol. Behav.* **147**, 324–33 (2015).
91652. Kim, J. W., Ha, G. Y. & Jung, Y. W. Chronic renal failure induces cell death in rat hippocampal
917 CA1 via upregulation of α CaMKII/NR2A synaptic complex and phosphorylated GluR1-
918 containing AMPA receptor cascades. *Kidney Res. Clin. Pract.* **33**, 132–8 (2014).
91953. Viggiano, D. *et al.* Quantifying barcodes of dendritic spines using entropy-based metrics. *Sci.*
920 *Rep.* **5**, 14622 (2015).
92154. Viggiano, D. *et al.* Information content of dendritic spines after motor learning. *Behav. Brain*
922 *Res.* **336**, 256–260 (2018).
92355. Kurella, M., Yaffe, K., Shlipak, M. G., Wenger, N. K. & Chertow, G. M. Chronic kidney
924 disease and cognitive impairment in menopausal women. *Am. J. Kidney Dis.* **45**, 66–76 (2005).
92556. Puy, L. *et al.* Cognitive Impairments and Dysexecutive Behavioral Disorders in Chronic
926 Kidney Disease. *J. Neuropsychiatry Clin. Neurosci.* **30**, 310–317 (2018).
92757. Yaffe, K. *et al.* Chronic Kidney Disease and Cognitive Function in Older Adults: Findings
928 from the Chronic Renal Insufficiency Cohort (CRIC) Cognitive Study. **58**, 338–345 (2011).
92958. Troen, A. M. *et al.* Cognitive dysfunction and depression in adult kidney transplant recipients:
930 baseline findings from the FAVORIT Ancillary Cognitive Trial (FACT). *J. Ren. Nutr.* **22**, 268-
931 76.e1–3 (2012).
93259. Vemuri, P. *et al.* Association of Kidney Function Biomarkers with Brain MRI Findings: The
933 BRINK Study. *J. Alzheimers. Dis.* **55**, 1069–1082 (2017).
93460. Drew, D. A. *et al.* Cognitive Decline and Its Risk Factors in Prevalent Hemodialysis Patients.
935 *Am. J. Kidney Dis.* **69**, 780–787 (2017).
93661. Lee, S. C. *et al.* The Association Between Kidney Function and Cognitive Decline in
937 Community-Dwelling, Elderly Japanese People. *J. Am. Med. Dir. Assoc.* **16**, 349.e1-349.e5
938 (2015).
93962. Griva, K. *et al.* Neuropsychological performance after kidney transplantation: A comparison
940 between transplant types and in relation to dialysis and normative data. *Nephrol. Dial.*
941 *Transplant.* **19**, 1866–1874 (2004).
94263. Hartung *et al.* Brain Magnetic Resonance Imaging Findings in Children and Young Adults
943 With CKD. *Am. J. Kidney Dis.* **72**, 349–359 (2018).

94464. Matsuda-Abedini, M. *et al.* Brain abnormalities in children and adolescents with chronic
945 kidney disease. *Pediatr. Res.* **84**, 387–392 (2018).
94665. Johnson, K. A., Fox, N. C., Sperling, R. A. & Klunk, W. E. Brain imaging in Alzheimer
947 disease. *Cold Spring Harb. Perspect. Med.* **2**, a006213 (2012).
94866. Giorgio, A. *et al.* Relevance of brain lesion location for cognition in vascular mild cognitive
949 impairment. *NeuroImage. Clin.* **22**, 101789 (2019).
95067. Lenzenweger, M. F. Thinking clearly about the endophenotype-intermediate phenotype-
951 biomarker distinctions in developmental psychopathology research. *Dev. Psychopathol.* **25**,
952 1347–57 (2013).
95368. Maung, S. C., El Sara, A., Chapman, C., Cohen, D. & Cukor, D. Sleep disorders and chronic
954 kidney disease. *World J. Nephrol.* **5**, 224–32 (2016).
95569. Kennedy, C., Ryan, S. A., Kane, T., Costello, R. W. & Conlon, P. J. The impact of change of
956 renal replacement therapy modality on sleep quality in patients with end-stage renal disease: a
957 systematic review and meta-analysis. *Journal of Nephrology* **31**, 61–70 (2018).
95870. Elias, R. M., Chan, C. T. & Bradley, T. D. Altered sleep structure in patients with end-stage
959 renal disease. *Sleep Med.* **20**, 67–71 (2016).
96071. Zoccali, C., Mallamaci, F. & Tripepi, G. Sleep apnea in renal patients. *J. Am. Soc. Nephrol.* **12**,
961 2854–9 (2001).
96272. Marrone, O. *et al.* Chronic kidney disease in European patients with obstructive sleep apnea:
963 the ESADA cohort study. *J. Sleep Res.* **25**, 739–745 (2016).
96473. Forni Ogna, V. *et al.* Prevalence and Diagnostic Approach to Sleep Apnea in Hemodialysis
965 Patients: A Population Study. *Biomed Res. Int.* **2015**, 103686 (2015).
96674. Huang, S.-T. *et al.* Risk, Severity, and Predictors of Obstructive Sleep Apnea in Hemodialysis
967 and Peritoneal Dialysis Patients. *Int. J. Environ. Res. Public Health* **15**, (2018).
96875. Tsampalieros, A. *et al.* Obstructive sleep apnea and hypertension in pediatric chronic kidney
969 disease. *Pediatr. Nephrol.* (2019). doi:10.1007/s00467-019-04295-7
97076. Nigam, G., Pathak, C. & Riaz, M. A systematic review of central sleep apnea in adult patients
971 with chronic kidney disease. *Sleep Breath.* **20**, 957–64 (2016).
97277. Tada, T. *et al.* The predictors of central and obstructive sleep apnoea in haemodialysis patients.
973 *Nephrol. Dial. Transplant* **22**, 1190–7 (2007).
97478. Zoccali, C., Mallamaci, F. & Tripepi, G. Nocturnal hypoxemia predicts incident cardiovascular
975 complications in dialysis patients. *J. Am. Soc. Nephrol.* **13**, 729–33 (2002).
97679. Zoccali, C., Mallamaci, F., Tripepi, G. & Benedetto, F. A. Autonomic neuropathy is linked to
977 nocturnal hypoxaemia and to concentric hypertrophy and remodelling in dialysis patients.
978 *Nephrol. Dial. Transplant* **16**, 70–7 (2001).
97980. Wennberg, A. M. V, Wu, M. N., Rosenberg, P. B. & Spira, A. P. Sleep Disturbance, Cognitive
980 Decline, and Dementia: A Review. *Semin. Neurol.* **37**, 395–406 (2017).

81. Matsunaga, Y. *et al.* Effects of zolpidem/triazolam on cognitive performance 12 hours after acute administration. *Sleep Med.* **52**, 213–218 (2018).
82. Suzuki, H. *et al.* Associations of Regional Brain Structural Differences With Aging, Modifiable Risk Factors for Dementia, and Cognitive Performance. *JAMA Netw. open* **2**, e1917257 (2019).
83. Viggiano, D. The hyperactive syndrome: metanalysis of genetic alterations, pharmacological treatments and brain lesions which increase locomotor activity. *Behav. Brain Res.* **194**, 1–14 (2008).
84. Aguilera, A., Sánchez-Tomero, J. A. & Selgas, R. Brain activation in uremic anorexia. *J. Ren. Nutr.* **17**, 57–61 (2007).
85. Tran, J., Ayers, E., Verghese, J. & Abramowitz, M. Gait abnormalities and the risk of falls in CKD. *Clin J Am Soc Nephrol* **14**, 983–993 (2019).
86. Arnold, R., Issar, T., Krishnan, A. V. A. A. V & Pussell, B. A. B. Neurological complications in chronic kidney disease. *JRSM Cardiovasc. Dis.* **5**, 2048004016677687 (2016).
87. Hamed, S. A. Neurologic conditions and disorders of uremic syndrome of chronic kidney disease: presentations, causes, and treatment strategies. *Expert Rev. Clin. Pharmacol.* **12**, 61–90 (2019).
88. Owolabi, L. F. *et al.* Related Factors and Predictors of Cognitive Dysfunction in Chronic Kidney Disease on Maintenance Hemodialysis in Nigeria. *J. Neurosci. Rural Pract.* **7**, S62–S67 (2016).
89. Hailpern, S. M., Melamed, M. L., Cohen, H. W. & Hostetter, T. H. Moderate chronic kidney disease and cognitive function in adults 20 to 59 years of age: Third National Health and Nutrition Examination Survey (NHANES III). *J. Am. Soc. Nephrol.* **18**, 2205–13 (2007).
90. Kumar, R. B. & Bhat, J. S. Voice in chronic renal failure. *J. Voice* **24**, 690–3 (2010).
91. Marquis, S. *et al.* Independent predictors of cognitive decline in healthy elderly persons. *Arch. Neurol.* **59**, 601–6 (2002).
92. Szczepańska-Gieracha, J., Cieślík, B., Chamela-Bilińska, D. & Kuczyński, M. Postural Stability of Elderly People With Cognitive Impairments. *Am. J. Alzheimers. Dis. Other Demen.* **31**, 241–6 (2016).
93. Tosto, G., Monsell, S. E., Hawes, S. E. & Mayeux, R. Pattern of extrapyramidal signs in Alzheimer’s disease. *J. Neurol.* **262**, 2548–56 (2015).
94. Hildebrandt, F. Genetic kidney diseases. *Lancet (London, England)* **375**, 1287–95 (2010).
95. Landini, S. *et al.* Reverse Phenotyping after Whole-Exome Sequencing in Steroid-Resistant Nephrotic Syndrome. *Clin. J. Am. Soc. Nephrol.* (2019). doi:10.2215/CJN.06060519
96. Verbitsky, M. *et al.* Genomic Disorders and Neurocognitive Impairment in Pediatric CKD. *J. Am. Soc. Nephrol.* **28**, 2303–2309 (2017).

101797. Caterino, M. *et al.* Urine Proteomics Revealed a Significant Correlation Between Urine-
1018 Fibronectin Abundance and Estimated-GFR Decline in Patients with Bardet-Biedl Syndrome.
1019 *Kidney Blood Press. Res.* **43**, 389–405 (2018).
102098. Körver, S. *et al.* Predictors of objective cognitive impairment and subjective cognitive
1021 complaints in patients with Fabry disease. *Sci. Rep.* **9**, 188 (2019).
102299. Sigurdardottir, S., Myers, S. M., Woodworth, J. M. & Raymond, G. V. Mental retardation and
1023 seizure disorder in Schimke immunoosseous dysplasia. *Am. J. Med. Genet.* **90**, 294–8 (2000).
1024100. Brancati, F., Dallapiccola, B. & Valente, E. M. Joubert Syndrome and related disorders.
1025 *Orphanet J. Rare Dis.* **5**, 20 (2010).
1026101. Liu, A. J. *et al.* Association of Cognitive and Behavioral Features Between Adults With
1027 Tuberous Sclerosis and Frontotemporal Dementia. *JAMA Neurol.* (2019).
1028 doi:10.1001/jamaneurol.2019.4284
1029102. Bökenkamp, A. & Ludwig, M. The oculocerebrorenal syndrome of Lowe: an update. *Pediatr.*
1030 *Nephrol.* **31**, 2201–2212 (2016).
1031103. Groopman, E. E. *et al.* Diagnostic Utility of Exome Sequencing for Kidney Disease. *N. Engl. J.*
1032 *Med.* **380**, 142–151 (2019).
1033104. Mengel-From, J. *et al.* Genetic Variants in KLOTHO Associate With Cognitive Function in the
1034 Oldest Old Group. *J. Gerontol. A. Biol. Sci. Med. Sci.* **71**, 1151–9 (2016).
1035105. Shardell, M. *et al.* Plasma Klotho and Cognitive Decline in Older Adults: Findings From the
1036 InCHIANTI Study. *J. Gerontol. A. Biol. Sci. Med. Sci.* **71**, 677–82 (2016).
1037106. Wuttke, M. *et al.* A catalog of genetic loci associated with kidney function from analyses of a
1038 million individuals. *Nat. Genet.* **51**, 957–972 (2019).
1039107. De Sanctis, C., Bellenchi, G. C. & Viggiano, D. A meta-analytic approach to genes that are
1040 associated with impaired and elevated spatial memory performance. *Psychiatry Res.* **261**, 508–
1041 516 (2018).
1042108. Moreno-Grau, S. *et al.* Genome-wide association analysis of dementia and its clinical
1043 endophenotypes reveal novel loci associated with Alzheimer’s disease and three causality
1044 networks: The GR@ACE project. *Alzheimers. Dement.* (2019).
1045 doi:10.1016/j.jalz.2019.06.4950
1046109. Hunter, D. J. & Drazen, J. M. Has the Genome Granted Our Wish Yet? *N. Engl. J. Med.* **380**,
1047 2391–2393 (2019).
1048110. Rodríguez-Rodríguez, E. *et al.* Genetic risk score predicting accelerated progression from mild
1049 cognitive impairment to Alzheimer’s disease. *J. Neural Transm.* **120**, 807–12 (2013).
1050111. Noguchi, Y., Nagasawa, H., Tachi, T., Tsuchiya, T. & Teramachi, H. Signal detection of oral
1051 drug-induced dementia in chronic kidney disease patients using association rule mining and
1052 Bayesian confidence propagation neural network. *Pharmazie* **74**, 570–574 (2019).
1053112. Jessen, N. A., Munk, A. S. F., Lundgaard, I. & Nedergaard, M. The Glymphatic System: A
1054 Beginner’s Guide. *Neurochem. Res.* **40**, 2583–2599 (2015).

1055113. Shah, S. V, Shukla, A. M., Bose, C., Basnakian, A. G. & Rajapurkar, M. Recent advances in
1056 understanding the pathogenesis of atherosclerosis in CKD patients. *J. Ren. Nutr.* **25**, 205–8
1057 (2015).
1058114. Ali, S., Dave, N., Virani, S. S. & Navaneethan, S. D. Primary and Secondary Prevention of
1059 Cardiovascular Disease in Patients with Chronic Kidney Disease. *Curr. Atheroscler. Rep.* **21**,
1060 32 (2019).
1061115. Bosch, A. *et al.* Retinal capillary and arteriolar changes in patients with chronic kidney disease.
1062 *Microvasc. Res.* **118**, 121–127 (2018).
1063116. Gennip, A. C. E. van *et al.* Endothelial dysfunction and low-grade inflammation in the
1064 transition to renal replacement therapy. *PLoS One* **14**, e0222547 (2019).
1065117. Lau, W. L. *et al.* Chronic Kidney Disease Increases Cerebral Microbleeds in Mouse and Man.
1066 *Transl. Stroke Res.* (2019). doi:10.1007/s12975-019-00698-8
1067118. Nortley, R. *et al.* Amyloid beta oligomers constrict human capillaries in Alzheimer’s disease
1068 via signaling to pericytes. *Science* (80-.). **365**, eaav9518 (2019).
1069119. Walker, K. *et al.* Association of midlife to late-life blood pressure patterns with incident
1070 dementia. *JAMA* **322**, 535–545 (2019).
1071120. Jiang, X. L. *et al.* Cerebral blood flow changes in hemodialysis and peritoneal dialysis patients:
1072 an arterial-spin labeling MR imaging. *Metab. Brain Dis.* **31**, 929–36 (2016).
1073121. Liu, H.-S. *et al.* Regional Cerebral Blood Flow in Children and Young Adults with Chronic
1074 Kidney Disease. *Radiology* **288**, 849–858 (2018).
1075122. Cheng, B.-C. *et al.* Decreased cerebral blood flow and improved cognitive function in patients
1076 with end-stage renal disease after peritoneal dialysis: An arterial spin-labelling study. *Eur.*
1077 *Radiol.* **29**, 1415–1424 (2019).
1078123. Moura, A. *et al.* Type of vascular access and location in online hemodiafiltration and its
1079 association with patient’s perception of health-related quality of life. *J. Vasc. Access* **15**, 175–
1080 82 (2014).
1081124. McGuire, S. *et al.* Hemodynamic Instability during Dialysis: The Potential Role of
1082 Intradialytic Exercise. *Biomed Res. Int.* **2018**, 8276912 (2018).
1083125. Polinder-Bos, H. A. *et al.* Hemodialysis Induces an Acute Decline in Cerebral Blood Flow in
1084 Elderly Patients. *J. Am. Soc. Nephrol.* **29**, 1317–1325 (2018).
1085126. Farhoudi, M., Abedi Azar, S. & Abdi, R. Brain hemodynamics in patients with end-stage renal
1086 disease between hemodialysis sessions. *Iran. J. Kidney Dis.* **6**, 110–3 (2012).
1087127. Tamura, M. K. *et al.* Chronic kidney disease, cerebral blood flow, and white matter volume in
1088 hypertensive adults. *Neurology* **86**, 1208–16 (2016).
1089128. Markus, H. S. Genes, endothelial function and cerebral small vessel disease in man. *Exp.*
1090 *Physiol.* **93**, 121–7 (2008).

1091129. Pabbidi, M. R. *et al.* Identification of a region of rat chromosome 1 that impairs the myogenic
1092 response and autoregulation of cerebral blood flow in fawn-hooded hypertensive rats. *Am. J.*
1093 *Physiol. Heart Circ. Physiol.* **304**, H311-7 (2013).
1094130. Fan, F. *et al.* Impaired myogenic response and autoregulation of cerebral blood flow is rescued
1095 in CYP4A1 transgenic Dahl salt-sensitive rat. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*
1096 **308**, R379-90 (2015).
1097131. Iliff, J. J. *et al.* A paravascular pathway facilitates CSF flow through the brain parenchyma and
1098 the clearance of interstitial solutes, including amyloid β . *Sci. Transl. Med.* **4**, 147ra111 (2012).
1099132. Rasmussen, M. K., Mestre, H. & Nedergaard, M. The glymphatic pathway in neurological
1100 disorders. *Lancet. Neurol.* **17**, 1016–1024 (2018).
1101133. Plog, B. A. & Nedergaard, M. The Glymphatic System in Central Nervous System Health and
1102 Disease: Past, Present, and Future. *Annu. Rev. Pathol.* **13**, 379–394 (2018).
1103134. Palmer, K., Mitolo, M., Burgio, F., Meneghello, F. & Venneri, A. Sleep Disturbance in Mild
1104 Cognitive Impairment and Association With Cognitive Functioning. A Case-Control Study.
1105 *Front. Aging Neurosci.* **10**, 360 (2018).
1106135. Menon, R. N. *et al.* Do quantified sleep architecture abnormalities underlie cognitive
1107 disturbances in amnesic mild cognitive impairment? *J. Clin. Neurosci.* **67**, 85–92 (2019).
1108136. Ju, Y.-E. S., Zangrilli, M. A., Finn, M. B., Fagan, A. M. & Holtzman, D. M. Obstructive sleep
1109 apnea treatment, slow wave activity, and amyloid- β . *Ann. Neurol.* **85**, 291–295 (2019).
1110137. Mawuenyega, K. G. *et al.* Decreased clearance of CNS beta-amyloid in Alzheimer's disease.
1111 *Science* **330**, 1774 (2010).
1112138. Li, C. *et al.* Roles of Neuropeptide Y in Neurodegenerative and Neuroimmune Diseases. *Front.*
1113 *Neurosci.* **13**, 869 (2019).
1114139. Baker, D. G. *et al.* Characterization of cerebrospinal fluid (CSF) and plasma NPY levels in
1115 normal volunteers over a 24-h timeframe. *Psychoneuroendocrinology* **38**, 2378–82 (2013).
1116140. Kastin, A. J. & Akerstrom, V. Nonsaturable entry of neuropeptide Y into brain. *Am. J. Physiol.*
1117 **276**, E479-82 (1999).
1118141. Zoccali, C. *et al.* Neuropeptide Y predicts cardiovascular events in chronic kidney disease
1119 patients: a cohort study. *J. Hypertens.* **37**, 1359–1365 (2019).
1120142. Barceló, A. *et al.* Neuropeptide Y and leptin in patients with obstructive sleep apnea syndrome:
1121 role of obesity. *Am. J. Respir. Crit. Care Med.* **171**, 183–7 (2005).
1122143. Zoccali, C. *et al.* Prospective study of neuropeptide y as an adverse cardiovascular risk factor
1123 in end-stage renal disease. *J. Am. Soc. Nephrol.* **14**, 2611–7 (2003).
1124144. Cannon, J. A. *et al.* Cognitive Impairment and Heart Failure: Systematic Review and Meta-
1125 Analysis. *J. Card. Fail.* **23**, 464–475 (2017).
1126145. Bründl, E. *et al.* Excessive release of endogenous neuropeptide Y into cerebrospinal fluid after
1127 treatment of spontaneous subarachnoid haemorrhage and its possible impact on self-reported

- 1128 neuropsychological performance - results of a prospective clinical pilot study on good. *Neurol.*
1129 *Res.* **40**, 1001–1013 (2018).
1130146. Choi, B. *et al.* Elevated Neuropeptide Y in Endothelial Dysfunction Promotes Macrophage
1131 Infiltration and Smooth Muscle Foam Cell Formation. *Front. Immunol.* **10**, 1701 (2019).
1132147. Lourida, I. *et al.* Parathyroid hormone, cognitive function and dementia: a systematic review.
1133 *PLoS One* **10**, e0127574 (2015).
1134148. Kellett, K. A., Williams, J., Vardy, E. R., Smith, A. D. & Hooper, N. M. Plasma alkaline
1135 phosphatase is elevated in Alzheimer's disease and inversely correlates with cognitive function.
1136 *Int. J. Mol. Epidemiol. Genet.* **2**, 114–21 (2011).
1137149. Díaz-Hernández, M. *et al.* Tissue-nonspecific alkaline phosphatase promotes the neurotoxicity
1138 effect of extracellular tau. *J. Biol. Chem.* **285**, 32539–48 (2010).
1139150. Vervloet, M. Renal and extrarenal effects of fibroblast growth factor 23. *Nat. Rev. Nephrol.* **15**,
1140 109–120 (2019).
1141151. McGrath, E. R. *et al.* Circulating fibroblast growth factor 23 levels and incident dementia: The
1142 Framingham heart study. *PLoS One* **14**, e0213321 (2019).
1143152. Kuro-O, M. The Klotho proteins in health and disease. *Nat. Rev. Nephrol.* **15**, 27–44 (2019).
1144153. Kuriyama, N. *et al.* Association between α -Klotho and Deep White Matter Lesions in the Brain:
1145 A Pilot Case Control Study Using Brain MRI. *J. Alzheimers. Dis.* **61**, 145–155 (2018).
1146154. Erickson, C. M. *et al.* KLOTHO heterozygosity attenuates APOE4-related amyloid burden in
1147 preclinical AD. *Neurology* **92**, e1878–e1889 (2019).
1148155. Nagai, T. *et al.* Cognition impairment in the genetic model of aging klotho gene mutant mice: a
1149 role of oxidative stress. *FASEB J.* **17**, 50–2 (2003).
1150156. Laszczyk, A. M. *et al.* FGF-23 Deficiency Impairs Hippocampal-Dependent Cognitive
1151 Function. *eNeuro* **6**,
1152157. Kosakai, A. *et al.* Degeneration of mesencephalic dopaminergic neurons in klotho mouse
1153 related to vitamin D exposure. *Brain Res.* **1382**, 109–17 (2011).
1154158. Cui, X., Gooch, H., Petty, A., McGrath, J. J. & Eyles, D. Vitamin D and the brain: Genomic
1155 and non-genomic actions. *Mol. Cell. Endocrinol.* **453**, 131–143 (2017).
1156159. Mayne, P. E. & Burne, T. H. J. Vitamin D in Synaptic Plasticity, Cognitive Function, and
1157 Neuropsychiatric Illness. *Trends Neurosci.* **42**, 293–306 (2019).
1158160. Goodwill, A. M. & Szoeki, C. A Systematic Review and Meta-Analysis of The Effect of Low
1159 Vitamin D on Cognition. *J. Am. Geriatr. Soc.* **65**, 2161–2168 (2017).
1160161. Sorrells, S. F. *et al.* Human hippocampal neurogenesis drops sharply in children to
1161 undetectable levels in adults. *Nature* **555**, 377–381 (2018).
1162162. Ma, D. K., Bonaguidi, M. A., Ming, G.-L. & Song, H. Adult neural stem cells in the
1163 mammalian central nervous system. *Cell Res.* **19**, 672–82 (2009).

1164163. Martino, G. & Pluchino, S. The therapeutic potential of neural stem cells. *Nat. Rev. Neurosci.* **7**,
1165 395–406 (2006).
1166164. De Feo, D., Merlini, A., Laterza, C. & Martino, G. Neural stem cell transplantation in central
1167 nervous system disorders: from cell replacement to neuroprotection. *Curr. Opin. Neurol.* **25**,
1168 322–33 (2012).
1169165. Meng, C., Zhang, J.-C., Shi, R.-L., Zhang, S.-H. & Yuan, S.-Y. Inhibition of interleukin-6
1170 abolishes the promoting effects of pair housing on post-stroke neurogenesis. *Neuroscience* **307**,
1171 160–70 (2015).
1172166. Wang, J. *et al.* Activated regulatory T cell regulates neural stem cell proliferation in the
1173 subventricular zone of normal and ischemic mouse brain through interleukin 10. *Front. Cell.*
1174 *Neurosci.* **9**, 361 (2015).
1175167. Widera, D., Mikenberg, I., Elvers, M., Kaltschmidt, C. & Kaltschmidt, B. Tumor necrosis
1176 factor alpha triggers proliferation of adult neural stem cells via IKK/NF-kappaB signaling.
1177 *BMC Neurosci.* **7**, 64 (2006).
1178168. Kokaia, Z., Martino, G., Schwartz, M. & Lindvall, O. Cross-talk between neural stem cells and
1179 immune cells: the key to better brain repair? *Nat. Neurosci.* **15**, 1078–87 (2012).
1180169. Liu, Q. *et al.* Neural stem cells sustain natural killer cells that dictate recovery from brain
1181 inflammation. *Nat. Neurosci.* **19**, 243–52 (2016).
1182170. Mohammad, M. G. *et al.* Immune cell trafficking from the brain maintains CNS immune
1183 tolerance. *J. Clin. Invest.* **124**, 1228–41 (2014).
1184171. Skardelly, M. *et al.* The influence of immunosuppressive drugs on neural stem/progenitor cell
1185 fate in vitro. *Exp. Cell Res.* **319**, 3170–81 (2013).
1186172. Rudenko, A. *et al.* Tet1 is critical for neuronal activity-regulated gene expression and memory
1187 extinction. *Neuron* **79**, 1109–1122 (2013).
1188173. Zhou, H., Wang, B., Sun, H., Xu, X. & Wang, Y. Epigenetic Regulations in Neural Stem Cells
1189 and Neurological Diseases. *Stem Cells Int.* **2018**, 6087143 (2018).
1190174. Posner, J. B., Plum, F., Saper, C. B. & Schiff, N. *Plum and Posner's Diagnosis of Stupor and*
1191 *Coma.* (Oxford University Press, 2007).
1192175. Kelly, D. M. The role of dialysis in the pathogenesis and treatment of dementia. *Nephrol. Dial.*
1193 *Transplant* **34**, 1080–1083 (2019).
1194176. Giang, L. M. *et al.* Cognitive function and dialysis adequacy: no clear relationship. *Am. J.*
1195 *Nephrol.* **33**, 33–8 (2011).
1196177. Lin, Y.-T. *et al.* Comparison of dementia risk between end stage renal disease patients with
1197 hemodialysis and peritoneal dialysis--a population based study. *Sci. Rep.* **5**, 8224 (2015).
1198178. Joshee, P., Wood, A. G., Wood, E. R. & Grunfeld, E. A. Meta-analysis of cognitive functioning
1199 in patients following kidney transplantation. *Nephrol. Dial. Transplant.* **33**, 1268–1277 (2018).
1200179. Gupta, A. *et al.* Cognitive Function and White Matter Changes Associated with Renal
1201 Transplantation. *Am. J. Nephrol.* **43**, 50–7 (2016).

1202180. SPRINT MIND Investigators for the SPRINT Research Group *et al.* Association of Intensive
1203 vs Standard Blood Pressure Control With Cerebral White Matter Lesions. *JAMA* **322**, 524–534
1204 (2019).
1205181. Brady, C. B. *et al.* Homocysteine lowering and cognition in CKD: the Veterans Affairs
1206 homocysteine study. *Am. J. Kidney Dis.* **54**, 440–9 (2009).
1207182. Abu Ahmad, N. *et al.* l-Carnitine improves cognitive and renal functions in a rat model of
1208 chronic kidney disease. *Physiol. Behav.* **164**, 182–8 (2016).
1209183. Farina, N., Isaac, M. G. E. K. N., Clark, A. R., Rusted, J. & Tabet, N. Vitamin E for
1210 Alzheimer’s dementia and mild cognitive impairment. *Cochrane database Syst. Rev.* **11**,
1211 CD002854 (2012).
1212184. Fujisaki, K. *et al.* Cerebral oxidative stress induces spatial working memory dysfunction in
1213 uremic mice: neuroprotective effect of tempol. *Nephrol. Dial. Transplant* **29**, 529–38 (2014).
1214185. Smith, P. J. & Blumenthal, J. A. Dietary factors and cognitive decline. *J. Prev. Alzheimer’s Dis.*
1215 **3**, 53–64 (2016).
1216186. Dearborn-Tomazos, J. L. *et al.* Association of Dietary Patterns in Midlife and Cognitive
1217 Function in Later Life in US Adults Without Dementia. *JAMA Netw. open* **2**, e1916641 (2019).
1218187. Vinothkumar, G., Krishnakumar, S., Riya & Venkataraman, P. Correlation between abnormal
1219 GSK3 β , β Amyloid, total Tau, p-Tau 181 levels and neuropsychological assessment total
1220 scores in CKD patients with cognitive dysfunction: Impact of rHuEPO therapy. *J. Clin.*
1221 *Neurosci.* **69**, 38–42 (2019).
1222188. Vinothkumar, G. *et al.* Therapeutic impact of rHuEPO on abnormal platelet APP, BACE 1,
1223 presenilin 1, ADAM 10 and A β expressions in chronic kidney disease patients with cognitive
1224 dysfunction like Alzheimer’s disease: A pilot study. *Biomed. Pharmacother.* **104**, 211–222
1225 (2018).
1226189. Wallace, H. J., Wallace, I. R. & McCaffrey, P. Cognitive decline reversed by cinacalcet. *Qjm*
1227 **108**, 59–61 (2015).
1228190. Ridker, P. M. *et al.* Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease.
1229 *N. Engl. J. Med.* **377**, 1119–1131 (2017).
1230191. Tardif, J.-C. *et al.* Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. *N.*
1231 *Engl. J. Med.* **381**, 2497–2505 (2019).
1232192. Liberale, L. *et al.* Post-ischaemic administration of the murine Canakinumab-surrogate
1233 antibody improves outcome in experimental stroke. *Eur. Heart J.* **39**, 3511–3517 (2018).
1234193. Sil, S., Ghosh, R., Sanyal, M., Guha, D. & Ghosh, T. A comparison of neurodegeneration
1235 linked with neuroinflammation in different brain areas of rats after intracerebroventricular
1236 colchicine injection. *J. Immunotoxicol.* **13**, 181–90 (2016).
1237194. Rahman, M. R. *et al.* Identification of molecular signatures and pathways to identify novel
1238 therapeutic targets in Alzheimer’s disease: Insights from a systems biomedicine perspective.
1239 *Genomics* (2019). doi:10.1016/j.ygeno.2019.07.018

1240195. Ferrari, C. C. *et al.* Progressive neurodegeneration and motor disabilities induced by chronic
1241 expression of IL-1beta in the substantia nigra. *Neurobiol. Dis.* **24**, 183–93 (2006).
1242196. Matsumoto, J. *et al.* TNF- α -sensitive brain pericytes activate microglia by releasing IL-6
1243 through cooperation between I κ B-NF κ B and JAK-STAT3 pathways. *Brain Res.* **1692**, 34–44
1244 (2018).
1245197. Furukawa, S., Usuda, K., Abe, M., Hayashi, S. & Ogawa, I. Indole-3-acetic acid induces
1246 microencephaly in mouse fetuses. *Exp. Toxicol. Pathol.* **59**, 43–52 (2007).
1247198. Adesso, S. *et al.* Indoxyl Sulfate Affects Glial Function Increasing Oxidative Stress and
1248 Neuroinflammation in Chronic Kidney Disease: Interaction between Astrocytes and Microglia.
1249 *Front. Pharmacol.* **8**, 370 (2017).
1250199. Fujita, Y. & Yamashita, T. The Effects of Leptin on Glial Cells in Neurological Diseases. *Front.*
1251 *Neurosci.* **13**, 828 (2019).
1252200. Segura, S. *et al.* Leptin-dependent neurotoxicity via induction of apoptosis in adult rat
1253 neurogenic cells. *Front. Cell. Neurosci.* **9**, 350 (2015).
1254201. Chun, H. J., Lee, Y., Kim, A. H. & Lee, J. Methylglyoxal Causes Cell Death in Neural
1255 Progenitor Cells and Impairs Adult Hippocampal Neurogenesis. *Neurotox. Res.* **29**, 419–31
1256 (2016).
1257202. Haddad, M. *et al.* Methylglyoxal and Glyoxal as Potential Peripheral Markers for MCI
1258 Diagnosis and Their Effects on the Expression of Neurotrophic, Inflammatory and
1259 Neurodegenerative Factors in Neurons and in Neuronal Derived-Extracellular Vesicles. *Int. J.*
1260 *Mol. Sci.* **20**, (2019).
1261203. Rizwan Siddiqui, M. *et al.* Erythropoietin-mediated activation of aquaporin-4 channel for the
1262 treatment of experimental hydrocephalus. *Childs. Nerv. Syst.* **34**, 2195–2202 (2018).
1263204. Liu, D. *et al.* Hydrogen sulfide promotes proliferation and neuronal differentiation of neural
1264 stem cells and protects hypoxia-induced decrease in hippocampal neurogenesis. *Pharmacol.*
1265 *Biochem. Behav.* **116**, 55–63 (2014).
1266205. Nath, N., Prasad, H. K. & Kumar, M. Cerebroprotective effects of hydrogen sulfide in
1267 homocysteine-induced neurovascular permeability: Involvement of oxidative stress, arginase,
1268 and matrix metalloproteinase-9. *J. Cell. Physiol.* **234**, 3007–3019 (2019).
1269206. Huang, T.-T., Hao, D.-L., Wu, B.-N., Mao, L.-L. & Zhang, J. Uric acid demonstrates
1270 neuroprotective effect on Parkinson's disease mice through Nrf2-ARE signaling pathway.
1271 *Biochem. Biophys. Res. Commun.* **493**, 1443–1449 (2017).
1272207. Yang, N., Xu, L., Lin, P. & Cui, J. Uric acid promotes neuronal differentiation of human
1273 placenta-derived mesenchymal stem cells in a time- and concentration-dependent manner.
1274 *Neural Regen. Res.* **7**, 756–60 (2012).
1275208. Moretti, R., Morelli, M. E. & Caruso, P. Vitamin D in Neurological Diseases: A Rationale for a
1276 Pathogenic Impact. *Int. J. Mol. Sci.* **19**, (2018).
1277209. Morello, M. *et al.* Vitamin D Improves Neurogenesis and Cognition in a Mouse Model of
1278 Alzheimer's Disease. *Mol. Neurobiol.* **55**, 6463–6479 (2018).

1279210. Watson, C. P. *et al.* The transporter and permeability interactions of asymmetric
1280 dimethylarginine (ADMA) and L-arginine with the human blood-brain barrier in vitro. *Brain*
1281 *Res.* **1648**, 232–242 (2016).
1282211. Luce, M. *et al.* Is 3-Carboxy-4-methyl-5-propyl-2-furanpropionate (CMPF) a Clinically
1283 Relevant Uremic Toxin in Haemodialysis Patients? *Toxins (Basel)*. **10**, (2018).
1284212. Leifheit-Nestler, M. & Haffner, D. Paracrine Effects of FGF23 on the Heart. *Front. Endocrinol.*
1285 (*Lausanne*). **9**, 278 (2018).
1286213. Huang, M. *et al.* The uremic toxin hippurate promotes endothelial dysfunction via the
1287 activation of Drp1-mediated mitochondrial fission. *Redox Biol.* **16**, 303–313 (2018).
1288214. Pu, T. *et al.* Persistent Malfunction of Glymphatic and Meningeal Lymphatic Drainage in a
1289 Mouse Model of Subarachnoid Hemorrhage. *Exp. Neurobiol.* **28**, 104–118 (2019).
1290215. Bird, M.-L., El Haber, N., Batchelor, F., Hill, K. & Wark, J. D. Vitamin D and parathyroid
1291 hormone are associated with gait instability and poor balance performance in mid-age to older
1292 aged women. *Gait Posture* **59**, 71–75 (2018).
1293216. Yang, S., Zhang, X., Yuan, J., Yin, J. & Hu, W. Serum Uric Acid is Independently Associated
1294 with Enlarged Perivascular Spaces. *Sci. Rep.* **7**, 16435 (2017).
1295217. Badran, M., Golbidi, S., Ayas, N. & Laher, I. Nitric Oxide Bioavailability in Obstructive Sleep
1296 Apnea: Interplay of Asymmetric Dimethylarginine and Free Radicals. *Sleep Disord.* **2015**,
1297 387801 (2015).
1298218. Obayashi, K. *et al.* Association of Serum Asymmetric Dimethylarginine With Muscle Strength
1299 and Gait Speed: A Cross-Sectional Study of the HEIJO-KYO Cohort. *J. Bone Miner. Res.* **31**,
1300 1107–13 (2016).
1301219. Gordon-Dseagu, V. L. Z. *et al.* The association of sleep with metabolic pathways and
1302 metabolites: evidence from the Dietary Approaches to Stop Hypertension (DASH)-sodium
1303 feeding study. *Metabolomics* **15**, 48 (2019).
1304220. Lee, W.-J. *et al.* Cystatin C, a potential marker for cerebral microvascular compliance, is
1305 associated with white-matter hyperintensities progression. *PLoS One* **12**, e0184999 (2017).
1306221. Yeh, Y.-C. *et al.* Indoxyl sulfate, not p-cresyl sulfate, is associated with cognitive impairment
1307 in early-stage chronic kidney disease. *Neurotoxicology* **53**, 148–152 (2016).
1308222. Beauchet, O. *et al.* Effects of Vitamin D and Calcium Fortified Yogurts on Gait, Cognitive
1309 Performances, and Serum 25-Hydroxyvitamin D Concentrations in Older Community-Dwelling
1310 Females: Results from the GAit, MEMory, Dietary and Vitamin D (GAME-D2) Randomized
1311 Controlled Trial. *Nutrients* **11**, (2019).

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1315 **Figure Legend**

1316 **Figure 1.** Schematic representation of the evolution of mild cognitive impairment (MCI) as a
 1317 function of CKD stage at fixed age (A) and as a function of age (B). The effect of replacement
 1318 therapies (HD, PD) in the end stage phase (ESRF) are also reported. A: The percent of mild
 1319 cognitive impairment, screened with tests such as the Mini Mental State Examination (MMSE)
 1320 or the Montreal Cognitive Assessment (MoCA), increases as a function of CKD stage/eGFR
 1321 (and possibly as a function of the time spent in that stage). B: the risk for MCI increases as a
 1322 function of time (age) in the general population. In patients with ESRF treated with
 1323 hemodialysis (HD) the risk remains greatly above the general population. Peritoneal dialysis
 1324 (PD) gives some advantage. Patients with mild CKD and kidney transplantation restores the
 1325 slope of the risk curve towards that of the general population; however, the initial gap
 1326 developed before transplantation is not “repaired” and therefore average cognitive
 1327 performances in transplanted patients remain below the non-CKD population. Lines are
 1328 estimates based on selected studies reported in Supplementary data. The confidence intervals
 1329 are derived from the variations among selected studies.

1330

1331 **Figure 2.** Schematic representation of brain modifications accompanying chronic kidney
 1332 disease (CKD), possibly mediated by uremic neurotoxins or lack of kidney neurotrophins.
 1333 Catecholamine neurons in the encephalic trunk/hypothalamus may be particularly sensitive to
 1334 the uremic milieu, thereby mediating the alterations in sleep patterns, mood, attention. These
 1335 may in turn impinge on memory, thus giving the emergence of Mild cognitive impairment
 1336 (MCI) and then dementia. LC: locus coeruleus. NE: norepinephrine neurons; 5HT: serotonin
 1337 neurons; DA: dopamine neurons; SN/VTA: Substantia Nigra/Ventral Tegmental Area; H:
 1338 histamine neurons; TM: tuberomammillary (hypothalamus), Ach: acetylcholine neurons; PFC:
 1339 prefrontal cortex.

1340

1341 **Figure 3.** The hierarchical organization connecting CKD to behavior. Cognitive impairment
 1342 is a complex behavioral pattern that can be screened using questionnaires and summarized in
 1343 a single score but is actually a multidimensional phenomenon comprising multiple cognitive
 1344 domains. Therefore, its relation with the direct effects of CKD (e.g. the biochemical changes
 1345 in plasma) is complex and difficult to understand. Intermediate phenotypes are quantitative
 1346 phenotypes connected to the complex behavioral alterations, but with simpler biological
 1347 substrates, which are more easily connected to the molecular derangements of CKD.

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1350 **Figure 4.** Uremic neurotoxins enter the brain via the blood brain barrier (BBB) and blood-
1351 CSF barrier (BCB) and leave the brain via the glymphatic system that is a polarized brain
1352 fluid transport system that connects with meningeal and peripheral lymphatic vessels for
1353 export of metabolic waste. CSF in the subarachnoid space is driven into the periarterial space
1354 by arterial pulsatility and mixes with interstitial fluid thus dragging waste product not only for
1355 export along the perivenous spaces but also within different areas of the brain including NPC
1356 niches, located within the sub granular (SGZ) zone and the sub ventricular zone (SVZ).
1357 Within these NPC niches uremic neurotoxins might interfere with proper functioning of
1358 endogenous NPCs, such as neurogenesis and homeostatic functions, thus further contributing
1359 perturb brain tasks during CKD.

1360

1361 **Figure 5.** Mechanism of action of some of the uremic (neuro)toxins and their interaction with
1362 genetic predisposing factors.

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5