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## Disorders of consciousness: responding to requests for novel diagnostic and therapeutic interventions

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*Lancet Neurol* 2012; 11: 732–38

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Severe brain injury can leave patients with chronic disorders of consciousness. Because of impaired responsiveness, many of these patients have traditionally been regarded as unaware. However, findings from recent clinical studies herald a potential paradigm shift: functional imaging and neurophysiological studies have identified ways to assess awareness and have revealed astounding cases of awareness despite clinical unresponsiveness. Hence, diagnostic classifications have been rewritten, prognostic knowledge is improving, and therapeutic studies have regained momentum, showing for the first time some therapeutic effects on responsiveness. Clinicians must increasingly respond to requests by patients' families and surrogate decision makers to use novel techniques for diagnosis, prognosis, and treatment, and in doing so several ethical and social issues need to be considered. Such requests provide an opportunity for clinicians to learn about patients' values and preferences and to maintain clinical acumen for changes in patient status with the patients' best interests in mind.

### Introduction

In recent years, advances in medical research have signalled a potential paradigm shift in the care of patients with unresponsive wakefulness syndrome (UWS, formerly known as the vegetative state)<sup>1</sup> and the minimally conscious state (MCS), collectively referred to as disorders of consciousness (DOC). Results of diagnostic studies have confirmed high rates of misdiagnosis<sup>2</sup> and have called into question existing diagnostic classifications by showing the presence of awareness in some patients whose clinical examination suggested otherwise.<sup>3,4</sup> Findings from pharmacological and surgical trials have shown effects of treatment on patients' levels of awareness.<sup>5–8</sup> As a result, clinicians such as neurologists, rehabilitation specialists, family doctors, nurses, and others must increasingly answer requests from family members and surrogate decision makers for novel diagnostic and therapeutic procedures that have been described in papers in peer-reviewed journals and widely reported in the media. Because these reported procedures remain investigational, clinicians must be aware of the level of evidence supporting them and of the unavoidable ethical and social issues involved in responding to such requests. We present a brief update on recent diagnostic and therapeutic advances in DOC and discuss the ethical and social aspects that should be considered in response to requests for new procedures. We hope that the perspective offered in this Personal View will stir discussion on the appropriate clinical care of patients with DOC in an evolving scientific context.

### An evolving neuroscience paradigm

The differential diagnosis of UWS and MCS is challenging and requires the use of specific behavioural scales that are validated for this purpose.<sup>9</sup> Without them, the rate of diagnostic error can be as high as 40%.<sup>2,10</sup> However, even with the most careful clinical assessment, some signs of awareness can be missed because the clinical diagnosis has to rely on motor signs of awareness

(non-reflex movements or motor response to commands) that can be very subtle and can fluctuate over time.

New technological developments make possible the direct measurement of brain function in both resting states and in response to simple commands, independent of muscle function. Resting-state functional MRI (fMRI) enables the quantification of residual connectivity in the brain's default-mode network,<sup>4</sup> which is thought to be involved in self-awareness (figure).<sup>11</sup> Automated analysis of PET images of the brain enables calculation of the probability of whether or not a patient is conscious.<sup>12</sup> Transcranial magnetic stimulation can trigger specific responses in electroencephalography (EEG) that seem to be characteristic of consciousness.<sup>13</sup>

Activation of specific brain regions in response to simple commands (eg, activation of the motor cortex after the command to imagine playing tennis) has been shown repeatedly on fMRI in some clinically vegetative patients, which suggests that these patients were probably conscious.<sup>3,14,15</sup> Similarly, findings from evoked potential studies showed that some patients without any clinical sign of awareness could count target words<sup>16</sup> or imagine moving their hand or foot,<sup>17</sup> as shown by event-related changes in EEG.

The incidence of such a “functional locked-in syndrome”, where only ancillary testing yields evidence of awareness, remains unclear. The cohorts in the published studies were small; thus, the reported frequencies of non-motor signs of command following in clinically vegetative patients (17% by fMRI<sup>3</sup> and 19% by evoked potentials<sup>17</sup>) should be interpreted with caution. Yet, in one case this technology permitted validated yes or no real-time communication using fMRI responses.<sup>3</sup> At the least, these findings shed substantial doubt on the accuracy of present clinical assessments and particularly their ability to rule out awareness. Developments in EEG-based brain–computer interfaces are improving quickly and the use of this technology will probably change the care of patients with DOC in the near future.

Whether differentiation of patients with MCS from those with UWS is useful is questionable, particularly because the presence of consciousness does not necessarily imply a change in the ethics of decision making.<sup>18,19</sup> In both disorders, patients have severe motor and cognitive impairments, remain fully dependent on others for all activities of daily living, and have no or very limited means to functionally communicate their thoughts or wishes. However, findings from functional imaging studies have shown that patients with MCS have partially preserved activation of emotion,<sup>20</sup> language,<sup>21</sup> and pain<sup>22</sup> networks in contrast to most patients with UWS. Also, chances of recovery and outcome in patients with MCS are thought to be better than in those with UWS.<sup>23</sup> Some patients with higher-level MCS have successfully participated in basic communication trials.<sup>24–26</sup>

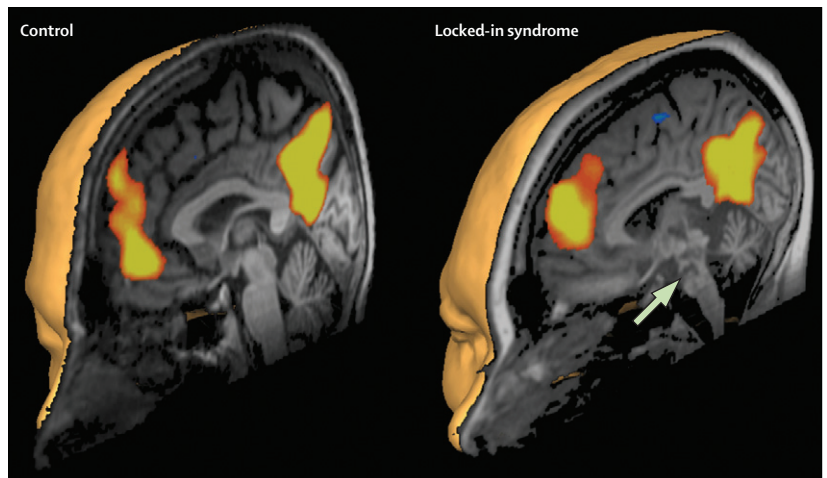
## New prognostic knowledge and therapeutic options

### Prognosis

Prognosis in patients with DOC can refer to life expectancy but most commonly is a measure of the likelihood of the return of full awareness and voluntary motor functions (neurological outcome). Clinicians should assess neurological outcome by applying guidelines and evidence from prospective studies to the individual case, considering the cause of brain damage, the duration of the present state, the biological age of the patient, and the presence of comorbidities. Prognosis should not rely merely on a patient's classification in a syndrome of UWS or MCS without also considering these individual factors.

In 1994, the Multi-Society Task Force on Persistent Vegetative State published its prognostic guideline,<sup>27</sup> which stated that a patient has a less than 1% probability of recovering awareness if he or she has survived without evidence of awareness for at least 3 months after a hypoxic–ischaemic neuronal injury or for at least 1 year after a traumatic brain injury (TBI). Although this guideline is still generally accepted, its accuracy is limited by two factors: first, the MCS was not a recognised entity before 2002, and some patients diagnosed with UWS were probably actually in an MCS; and second, the patient databases relied upon by the Task Force to determine life expectancy were probably affected by the fallacy of the self-fulfilling prophecy—that is, outcomes were negatively biased because the databases included many patients whose life-sustaining therapy was discontinued by their physicians on the grounds of an assumed poor prognosis.<sup>28</sup>

Some studies have reported a better prognosis than that predicted by the Multi-Society Task Force. Estraneo and colleagues<sup>29</sup> reported that 12% of patients with UWS recovered awareness after the 3-month or 12-month threshold (as stated by the Task Force), including one patient who regained awareness 22 months after a hypoxic–ischaemic injury. Despite recovering awareness, these patients remained severely disabled after their



**Figure: Functional neuronal connectivity in a conscious control and a patient with locked-in syndrome** Resting-state functional MRI recordings show the functional integrity of the so-called default mode network, which is thought to be involved in internal awareness, mind wandering, and inner speech. The yellow areas show functional neuronal connectivity in the anterior cingulate, mesiofrontal and posterior cingulate, and precuneal cortices in a conscious control (left) and in a patient with locked-in syndrome or pseudo-coma (right). The arrow points to the structural damage (hypodensity after stroke) in the pontine brainstem area. The images are the product of an independent component analysis, based on data from the study by Soddu and colleagues,<sup>31</sup> in which participants were instructed to keep their eyes closed and remain awake without undertaking any other task. Resting-state blood oxygen level-dependent (BOLD) changes were measured on a 3-Tesla MRI scanner with a gradient echo-planar sequence (Trio Tim Siemens, Germany). The blue area signifies anticorrelations to the default mode network.

injuries. Luauté and colleagues<sup>23</sup> reported that a third of the patients with MCS in their series improved 1 year after their injuries. Thus, patients with DOC probably can improve after time intervals longer than those established by the Multi-Society Task Force.

Functional neuroimaging can also provide information on prognosis. The patient with TBI described by Owen and colleagues<sup>15</sup> who exhibited wilful modulation of brain activity, despite being clinically diagnosed as UWS by able examiners, began to show clinical signs of awareness 11 months after her injury. Similarly, the two patients with UWS described by Di and colleagues<sup>30</sup> who showed activation of the perisylvian cortical language region after hearing a voice say their name were the only patients with UWS in their series who later recovered clinical signs of awareness. Thus, the subgroup of patients with clinically diagnosed UWS in whom fMRI shows activation patterns suggestive of awareness might be those who are destined to regain clinical evidence of awareness.<sup>31</sup>

### Treatment

The standard treatment for patients with DOC is neurorehabilitation, and the general clinical impression is that targeted rehabilitative therapy in specialised units probably improves outcome.<sup>32</sup> Several stimulation treatments have been used in an attempt to improve the recovery of awareness in patients with DOC. Treatment protocols providing sensory stimuli including sounds, words, visual images, touch, and smells are widely prescribed, although there is little

high-grade evidence from controlled trials that they are effective in promoting recovery.<sup>33</sup>

Several drug trials have been done with the aim of stimulating thalamic neurons that have been spared by the global injury that causes UWS or MCS. Among those most commonly prescribed are levodopa and dopamine agonists such as amantadine, but also sympathomimetic drugs and zolpidem.<sup>6,7,34</sup> Most drug trials for which data have been published were uncontrolled. However, in a recent randomised controlled trial,<sup>8</sup> amantadine improved the rate of functional recovery in patients with DOC after TBI compared with placebo. Contrary to the belief that patients with MCS respond more favourably to drug treatments than those with UWS, this trial showed similar responses to amantadine in both patient groups.<sup>8</sup>

For over 20 years, electrical deep brain stimulation (DBS) in the thalamus has been done in an attempt to induce awareness in DOC but has not shown efficacy except in a few uncontrolled case reports.<sup>35</sup> In a case report of DBS of the intralaminar thalamic nuclei, a man who had been in a stable MCS for 6 years showed significant improvement in his responsiveness, language, and arousal when the stimulator was turned on, with return to baseline poor responsiveness when it was turned off.<sup>9</sup> At present, all trials of DBS in DOC are classified as experimental.

The medical decision to stop rehabilitation and transfer a patient to a long-term care facility can be hard to accept for the family, but one of the most difficult treatment decisions by family members is whether to continue life-sustaining therapy or to discontinue it and provide palliative care. Neurologists and other clinicians can have difficulties understanding the notions of valid consent and refusal of therapy.<sup>36</sup> The few patients with clinical UWS who have exhibited wilful modulation of brain activity on fMRI and have thereby been able to communicate yes or no responses<sup>3</sup> probably do not possess the legal capacity to fully consent to or refuse life-sustaining treatment because of remaining cognitive

deficits and the limits and uncertainties of this communication technique.<sup>19</sup> However, in cases where the cognitive status and prognosis of a patient with DOC is shown by functional imaging to be better than assumed, more rehabilitation efforts might be warranted.<sup>23</sup>

### Ethical and social aspects of requests for novel interventions

The advances in research and clinical care of patients with DOC have increased public awareness so that family members and health-care surrogate decision makers might ask clinicians to order novel diagnostic examinations and therapeutic interventions on the basis of findings from studies published in peer-reviewed journals or reports in the popular media. We propose several points for health-care professionals to consider when responding to such requests (panel).

#### Diagnosis

##### *Recognise the value and limitations of new technology*

Recent reports have confirmed the limitations of conventional clinical assessments in establishing the diagnosis and prognosis of patients with DOC.<sup>2,37</sup> New brain imaging techniques have exposed inconsistencies in clinical assessments, are a valuable aid in confirming or refuting clinical diagnoses, and provide additional prognostic information.<sup>3,30,38</sup> At present, the available evidence does not warrant the use of functional imaging assessments in routine care for all patients. These assessments can show only neural correlates of cognitive functions. However, the research value of such techniques to better objectify diagnosis and prognosis is increasingly being recognised. Active research and treatment centres, where the imaging technology and expertise are available or could be developed, should start trialling these assessments as a means to verify challenging diagnoses, monitor diagnostic accuracy, and help family members and surrogate decision makers to understand more precisely the neurological status of their loved one.<sup>39</sup> Moreover, simpler and more widely available technologies such as EEG and evoked potential tests<sup>17,40</sup> could lower the barriers of cost and expertise and support a call for more widespread adoption of novel technologies in routine care. Large prospective studies should be done to assess the clinical value of these technologies and identify which technique is indicated for which type of patient, depending on the cause of DOC, duration, and clinical characteristics. The cost effectiveness of such procedures is not established and merits further attention in the context of limited resources. The average costs of care for patients with DOC are high but might be ethically justified in view of the low prevalence of such disorders.<sup>41,42</sup>

##### *Clarify hopes and expectations, taking into account the strain on family members*

Family members and surrogate decision makers might approach clinicians with unrealistic expectations about

#### **Panel: Points to consider when responding to requests for novel diagnostic and therapeutic interventions in disorders of consciousness**

##### **Diagnosis**

- Recognise the value and limitations of new technology
- Clarify hopes and expectations, taking into account the strain on family members
- Acknowledge the complex ethical relation between patient awareness and decision making
- Use adequate language for describing syndromes

##### **Prognosis and treatment**

- Communicate prognosis in an area of uncertainty
- Involve patients and their families in research studies
- Publish individual case reports responsibly
- Approach treatment decision making by focusing on goals of treatment

new technologies. They might view advanced diagnostic procedures as the ultimate proof: the procedure that will allow them definitively to establish whether the patient is aware or predict the time of recovery. Research into media coverage of functional imaging technologies has identified shortcomings in publicly available information.<sup>43</sup> First, these techniques are rarely explained and, when they are, the quality of the explanations is often poor.<sup>43,44</sup> Second, several misunderstandings about the capabilities of neuroimaging are common in media coverage (eg, imaging technologies provide a direct picture of brain activity, are simple to interpret, or provide more powerful evidence than clinical assessment per se).<sup>43,45</sup> These misunderstandings might partly explain why imaging evidence confers such a high authority to scientific explanations in the eyes of the public.<sup>46,47</sup> Clinicians should be aware of these misunderstandings and therefore explain the nature of advanced imaging as well as the diagnostic uncertainty that might remain even after the tests.<sup>48</sup>

Imaging results might help families and surrogate decision makers to understand clinical realities and cope with the limited prospects of recovery; however, nurturing false hopes can also harm families and patients (table). The possibility of false-negative and false-positive results must be taken into account, especially in view of the novelty of the technology and the fluctuating states of the patients, which call for repeated measures over time.<sup>49</sup> How the detection of awareness in a patient affects the family members and surrogate decision makers should be investigated to understand its consequences for relationships, behaviours, and decision making. For example, if a patient is shown to be aware, do family members speak to and handle the patient differently? By contrast, if a patient is shown to be irreversibly unaware, will that help family members to accept reality and facilitate the mourning process? The latter might be a major reason why relatives want to have these tests in the first place.

*Acknowledge the complex ethical relation between patient awareness and decision making*

Although signs of awareness detected through advanced imaging might intuitively suggest a specific ethical stance on treatment decision making (ie, arguing for continued life-sustaining treatment and intensified rehabilitation efforts),<sup>50</sup> this relation is much more complex.<sup>18,19</sup> First,

detection of some cognitive function might not equate with fully intact awareness. Second, continuing treatment might not be the patient's preference or the surrogate decision maker's understanding of the patient's wishes, especially because patients with MCS might experience pain or suffering.<sup>51</sup> Third, if the preferences of the patient cannot be ascertained, awareness in itself does not necessarily mean that preserving life is always in the patient's best interests.<sup>18,41,52</sup> As with all treatment decisions, patient preferences, prognosis, and the ability to further the patient's wellbeing should be key, with advanced imaging being incorporated into a framework of shared decision making.<sup>53</sup>

*Use adequate language for describing syndromes*

Some clinicians and family members have complained about the seemingly pejorative nature of the terms (encountered in many languages) used to describe DOC.<sup>54</sup> The term vegetative was coined 40 years ago to describe the continuation of automatic activities in non-responsive patients.<sup>55</sup> More recently, alternative terms have been suggested, including post-coma unresponsiveness<sup>56</sup> and UWS.<sup>1</sup> These names more precisely and neutrally describe the clinical status and perhaps imply more respect for the patients, their loved ones, and the relationships between them. In view of the limitations of clinical assessments, more sensitive terminology could help to preserve trust in clinicians and encourage a mutually respectful relationship. Furthermore, because of common misunderstandings about DOC in the public domain,<sup>57-59</sup> family members and surrogate decision makers should be offered basic information about the nature of these disorders.

**Prognosis and treatment**

*Communicate prognosis in an area of uncertainty*

Communicating prognosis to the patient's family members is a crucial part of clinical care and needs to be repeated over time, particularly as the clinical state changes or as new test results are obtained. Prognosis should be evidence-based, yet adapted to the individual characteristics of the patient. Single reports of late recoveries and treatment effects in the scientific or lay media should be taken seriously, but judicious examination of such reports might reveal issues of misdiagnosis, misreporting, and spontaneous recovery.<sup>60</sup>

	Beneficial effects	Harmful effects
Tests show less brain activity than found on neurological examination	Relatives might cope better with the decision to withdraw life-sustaining treatment	Relatives might lose hope, purpose, and meaning in life
Tests show more brain activity than found on neurological examination	Clinical management might be intensified by the chance of further recovery	False hopes might be nurtured, leading to long-term harm, disappointment, and suffering
Tests show the same level of brain activity as found on neurological examination	Clinicians and relatives might be affirmed in their decision about the level of treatment	Clinicians and relatives might be disappointed and treatment cost effectiveness might be poor

Tests include, for example, functional MRI and electroencephalography.

**Table: Results of additional diagnostic testing and their possible ethically relevant effects**



Prognosis is a statistical concept. Prognostic accuracy is greater when determining the mean neurological outcome for a group of similar patients than for any individual patient within that group. Individual neurological outcomes can be expressed only in standard deviations from the mean. However, statistical information might not be satisfying to the patient's family members, who want to know with greater exactitude whether or not their loved one will recover neurologically.<sup>61</sup> In an area of unavoidable uncertainty like this, physicians should frankly admit the uncertainty to enable autonomous decisions and foster trustful relationships with families and surrogate decision makers.

Moreover, when discussing their prognostic assessment with a patient's family members or surrogate decision maker, physicians should ensure that communication is not affected by their own bias about treatment and quality of life in disability.<sup>62</sup> Some patients and their families might judge moderate or severe disability to be an acceptable outcome even if their clinicians do not, and vice versa.<sup>63</sup> Families should be instructed about the first signs of recovery (eg, visual pursuit, localisation to noxious stimulation, contingent behaviour to specific emotionally salient stimuli, and motor response to commands) but also be informed that any recovery will probably be slow and the person will remain significantly disabled and most often dependent on others for all activities of daily life.

#### *Involve patients and their families in research studies*

In view of present knowledge gaps in prognosis and treatment, development and funding of research is paramount, and patients and their families should be offered the opportunity to participate in clinical studies. Because of the low incidence of DOC, collaborations between research centres will be needed to develop population-based disease registries, prospective longitudinal outcome studies, and multicentre randomised controlled treatment trials with long-term follow-ups.

The results of research studies promise new knowledge to improve the care of future patients, but research

#### **Search strategy and selection criteria**

We searched and reviewed literature in PubMed, published between April, 2002, and April, 2012, using various combinations of the following keywords: "disorders of consciousness", "vegetative state", "minimally conscious state", "diagnosis", "prognosis", "treatment", "communication", "ethics", and "end-of-life decisions". Articles were also identified from manual searches of reference lists and the authors' own files. Only articles written in English were included. The authors selected key contributions published in leading journals on the basis of expert judgment and tailored to the requirements of a Personal View article.

participants might also benefit. Because regular examinations are undertaken during such studies, clinical improvements might be detected earlier and more reliably, especially since many DOC patients live in long-term care facilities in which they rarely undergo neurological tests.<sup>64</sup> Consent from surrogate decision makers and procedural safeguards are needed ethically, but patients with DOC should not be excluded from research.<sup>39</sup> High-risk interventional treatment, such as deep brain stimulation, should be restricted to centres with specific expertise, undertaken within trials, and accompanied by special ethical assessment.<sup>65</sup> Off-label drug use might be justified if the approach has a clear rationale, the risks are low, and proper safeguards are in place.<sup>66</sup>

#### *Publish individual case reports responsibly*

Most scientific and lay reports of treatment effects or of late recovery feature individual cases. They are therefore difficult to compare and do not provide the robust evidence necessary for treatments to become standard care. If a treatment effect is seen outside a regular trial, the best approach is to document the effect properly and submit a paper on the case to a peer-reviewed scientific journal. Clinicians and researchers should be careful not to raise unsubstantiated hopes in the general public when reporting individual cases to the lay media. Yet, carefully and responsibly informing the public respects the needs of other patients and families, promotes public awareness, and can advance both DOC research and health care.

#### *Approach treatment decision making by focusing on goals of treatment*

In most cases of DOC, the question eventually arises of whether life-sustaining treatment should be continued. Shared decision making, a relationship of trust, and excellent communication skills between physicians and surrogate decision makers are essential to promote conditions for ethical medical practice, prevent undue psychological burden on surrogate decision makers, and avoid legal complications.<sup>67,68</sup> Family caregivers often show fluctuating attitudes because of their ambivalent emotions.<sup>69</sup> Depression in caregivers culminates roughly 3 years after the injury and is particularly prevalent in parents of young patients.<sup>70</sup> Clinicians should take this factor into account, provide compassionate counselling to the patient's family, and offer them emotional support.<sup>71</sup> Physicians need to be aware that their own moral attitudes might differ from those of the surrogate decision makers.<sup>10,72</sup>

Decision making is optimised when it focuses on the goals of care. These goals can range from the recovery of functional independence to the palliation of suffering while accepting death. In some circumstances, a request for further investigation can become an opportunity to discuss the goal of care. Treatment is ethically justified if there is a realistic chance to achieve the goal and if it aligns with the patient's preferences, which might be evidenced by a living will or by the substituted judgment

of a proxy.<sup>41</sup> Behavioural signs of wellbeing should not be mistaken for expressions of will—an error that often occurs in the care of neurologically impaired patients.<sup>69,73</sup> If a decision is made to discontinue life-sustaining treatment, which usually means stopping artificial nutrition and hydration, appropriate palliative care has to be provided. In cases in which the awareness of the patient remains in doubt, a palliative care plan will encompass pain and symptom management on the basis of the patient's physical signs.

## Conclusions

Because family members might learn about new investigational procedures in media reports, clinicians need to be prepared to discuss recent evidence about DOC in the context of shared decision making with ethical sensitivity. We have reviewed recent advances in DOC research and formulated suggestions from a personal perspective on how to respond to requests for such procedures. We adopt the approach that such requests offer a shared opportunity for clinicians and family members to build a respectful relationship.<sup>74</sup> By listening to family members, clinicians can learn about the patient's values and preferences and maintain clinical acumen for changes in patient status with the best interests of the patient in mind. Family members can be updated on the nature of DOC and can be engaged in decisions for further examination, research studies, clinical investigations, or in some cases palliative care. We acknowledge that a proper response is shaped by ongoing progress in research and characterised by the integration of scientific, medical, and ethical considerations.

### Contributors

RJJ and ER wrote the section on ethical and social aspects, the background, summary and concluding statement, and coordinated the work. SL wrote the section on the evolving neuroscience paradigm, and JLB wrote the section on new prognostic knowledge and therapeutic options. All authors revised the whole paper.

### Conflicts of interest

SL is Senior Research Associate of the Belgian National Funds for Scientific Research (FRS). All other authors declare that they have no conflicts of interest.

### Acknowledgments

RJJ's work is funded by the German Ministry for Research and Education. ER thanks members of the Neuroethics Research Unit for useful feedback on a previous version of this manuscript and acknowledges funding from the Canadian Institutes of Health Research (New Investigator Award and Tri-lateral Neuroethics Initiative). The funding agencies were not involved in the preparation of this article. We thank Dorothee Wagner von Hoff for proofreading the manuscript.

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