Anosognosia in patients during transient hemispheric anesthesia

Master Thesis

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Abstract

Individualized functional mapping before epilepsy surgery is important, as the localization of function is variable among patients and may be influenced by epilepsy. The “golden standard” in testing language lateralization is the Wada test. During this procedure a major part of a hemisphere is temporarily inactivated. We can therefore expect contralateral hemiparesis and often (incomplete) hemianopia. Patients may not recall this hemiparesis when asked a few minutes after the test. The denial or inability to recognize the presence of such a major physical impairment can be seen as a form of anosognosia. The underlying mechanism for such anosognosia, lasting up to a few minutes after hemispheric anesthesia during the Wada test, has not been studied. The current study will investigate how often a patient, a few minutes after the Wada injection, is not aware of an inability during the test and if this anosognosia can be profiled. We expect that anosognosia will occur when the non-language-dominant hemisphere is anesthetized and the patient has a pre-existing deficit in executive functioning. In addition to testing this hypothesis, explorative research will also be conducted to see if there are multiple remarkable observations to form new hypotheses in the future. Video recordings of the Wada tests were reviewed. Symptoms of anosognosia was present in 70% of the cases. We could not find an association between a range of presumed predictive variables and the occurrence of anosognosia. Only a trend for male sex is found.

Introduction

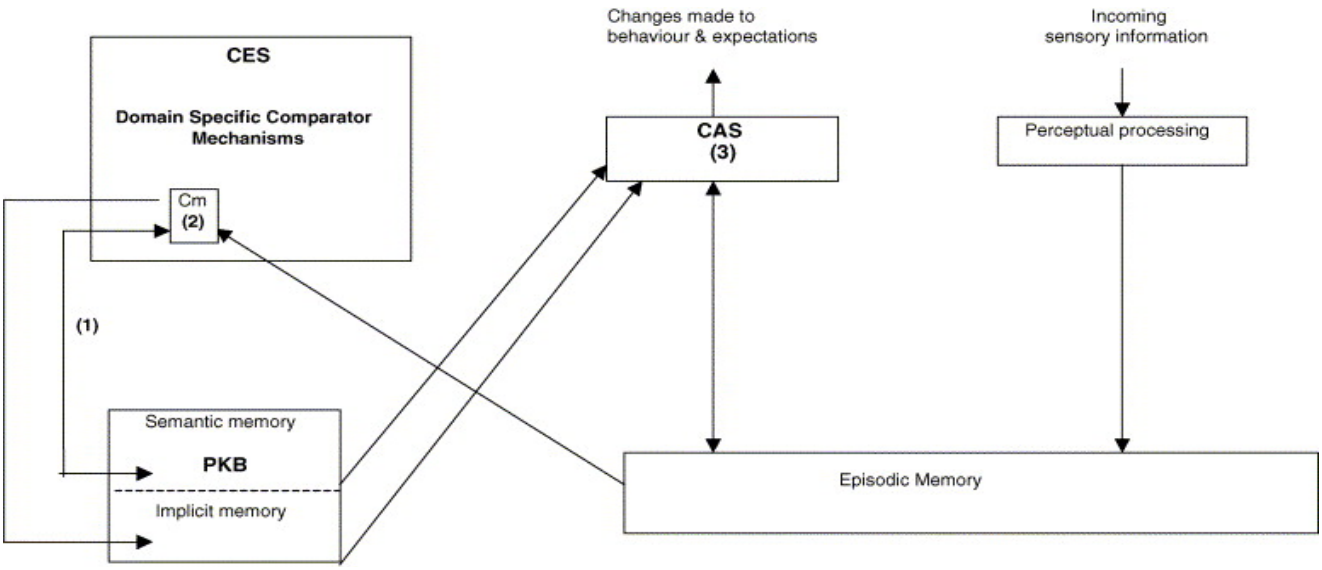
Worldwide more than 65 million people suffer from epilepsy. It is, therefore, one of the most common chronic neurological diseases (Moshé, Perucca, Ryvlin, & Tomson, 2015). Epilepsy causes not only seizures but also cognitive decline, reduced quality of life, and reduced life expectancy (Grote, et al., 2016). In addition to a large spectrum of anti-seizure drugs, the number of patients who undergo brain surgery for epilepsy is growing. Surgery can be beneficial for the people who have drug-resistant focal epilepsy (Moshé, et al., 2015; Van Zandvoort, Ruis & Hendriks, 2016) and give a considerable chance of seizure reduction. Research shows that more than half of patients are seizure-free after surgery. It is important that the patient will not suffer cognitive impairments or behavioral and emotional problems as an unwanted side-effect of surgery (Bremm, Grewe, Bien, & Hendriks, 2019). Individualized functional mapping before epilepsy surgery is important, as the localization of function is variable among patients and may be influenced by epilepsy (Chang et al., 2017).

Usually, the left hemisphere is dominant for language, praxis and motor control of the right hand, whereas the right hemisphere is specialized in the control of visuospatial skills and spatial attention. This lateralization does not apply to everyone (Zago et al., 2017), which became evident in a study by Woerman et al (2003), showing that 30% of epilepsy patients have atypical language lateralization, viz. right-sided or bilateral dominance. Similarly, more than half of the patients with a left-hemispheric stroke suffer from spatial neglect, while it is common that the right hemisphere is dominant for surveillance and orientation (Flöel et al., 2004). Patients with neglect have a failure to report events or stimuli occurring in hemispace through a loss of awareness when an overall spatial perception is formed (Danckert & Feber, 2006). In some cases the left hemisphere may be critical for attention, just as the right hemisphere may be for language (Flöel et al., 2004). These are important considerations when planning brain surgery in potentially critical areas. In the work-up for epilepsy surgery, establishing hemispheric dominance is routine.

Language lateralization can be established in several ways. It is possible to test for language during surgery, either through monitoring language performance during resection or, before resection, but with the cortex exposed, by mapping eloquent areas by electrocortical stimulation and establishing sites that interfere with language tasks. Different tests can be used like naming objects (De Witte, et al., 2016). Testing during surgery has saved many patients from postoperative cognitive impairment (Van Zandvoort, Ruis & Hendriks, 2016). But intraoperative testing is cumbersome, involves a specialist neuropsychologist, increases surgical risks and puts the patient under extra stress. Intraoperative language testing as a routine

has therefore never gained popularity. The current alternative "golden standard" in testing language lateralization is the Wada test, named after its inventor Jun Wada (Szantroch, 2019), that can be performed presurgically. In this procedure, a major part of a hemisphere is temporarily inactivated by injecting a short-acting neurosuppressive drug through an intra-arterial catheter. The catheter is inserted in the iliac artery and guided into the internal carotid artery by Seldinger angiography. The other hemisphere will stay awake and functioning, in spite of redistribution after first pass (Tu et al, 2015). Within seconds after drug injection into the internal carotid, there will be contralateral hemiplegia and if the language dominant hemisphere is injected, a language deficit. The involved hemisphere will recover after a few minutes with the return of functions (Kundu, Rolston & Grandhi, 2019). With the Wada test, the neuropsychologist can reliably predict the absence of major language deficits after surgery (Blackmon, 2016; Kho et al., 2005). Moreover, the Wada test may reveal residual memory capacity of the contralateral hemisphere if one tests for memory as well during the test protocol (Blackmon, 2016; Woerman et al, 2003).

By injecting the internal carotid, the short-acting drug will distribute itself mainly in the ipsilateral area vascularized by the medial cerebral artery, often also the anterior cerebral artery (depending on completeness the Willis' circle) and rarely the posterior cerebral artery that is usually filled by the vertebrobasillar artery. The medial cerebral artery is the main supply of both Broca's and Wernicke's area and the white matter tracts going through the temporal lobe, such as Meyer's loop. During the Wada test, we can therefore expect contralateral hemiparesis and often (incomplete) hemianopia. Hemiparesis is revealed as patients are asked to raise their hands before injection, and the contralateral arm will drop. Patients may not recall this hemiparesis when asked a few minutes after the test. The denial or inability to recognize the presence of such a major physical impairment is a form of anosognosia (Meador, Loring, Feinberg & Nichols, 2000).



Note. **(1)** = Mnemonic anosognosia; **(2)** = Executive anosognosia; **(3)** = Primary anosognosia; **CES** = Central Executive System; **Cm** = Comparator mechanisms; **PKB** = Personal knowledge base; **CAS** = Conscious awareness system.

Figure 1. Dissociable interactions and conscious experience model (adapted from Agnew and Morris, 1998)

Normally a person becomes aware of a mismatch between the incoming information about a recent failure and existing information about person's ability through links between the comparator mechanisms (Cm), the episodic memory and the conscious awareness system (CAS). To explain anosognosia a cognitive framework is proposed, see Figure 1. Incoming information about a recent failure first enters episodic memory. Subsequently, this information is passing to the conscious awareness system (CAS). At the same time, the information is monitored by comparator mechanisms that contrast it with existing information about the person's current function which is stored in the semantic personal knowledge base (PKB). If a mismatch occurs between the performance information and the contents of the PKB, the PKB is updated via input from episodic to semantic memory (Ansell & Bucks, 2006; Morris & Mograbi, 2013). Research into Alzheimer's disease shows that three different deficits in this system can lead to anosognosia: a deficit in the pathway between the Cm and the semantic memory results in the PKB being unable to update (mnemonic anosognosia), a deficit in the Cm itself results in not being able to compare the performance with the PKB, which leads to a lack of awareness of the impairment (executive anosognosia) and an impairment of the CAS results in unawareness of the state of functioning in all domains (primary anosognosia).

Hemibody or hemispatial anosognosia is often associated with the right hemisphere, but it seems that anesthesia of the left hemisphere can also produce anosognosia which is less easy to detect (Cocchini, Beschin & Della Sala, 2018). The underlying mechanism for such

anosognosia, lasting up to a few minutes after hemispheric anesthesia during the Wada test, has not been studied (Meador et al., 2000). In stroke patients, neuroimaging studies revealed no specific pattern of brain injury or dysfunction that is selectively associated with anosognosia. Anosognosia for hemiplegia appears to be associated with a wide network of areas, including areas of the frontal, temporal and parietal cortices (Moro et al., 2016).

Earlier studies of anosognosia found inconsistent results. This may be due to differences in patient selection and methodology (Moro et al., 2016). In our current study, we studied epilepsy patients during the Wada procedure, up to 15 minutes after injection of the short-acting barbiturate methohexital. The only other study of anosognosia related to the Wada test is by Meador et al. (2000). This study shows that anosognosia commonly occurs with acute inactivation of the non–language-dominant hemisphere, usually the right hemisphere except for patients with a right hemisphere language dominance as established by the same test (Meador et al., 2000). In this study there was just one patient with right cerebral language-dominance (Meador et al., 2000). Our study will involve more patients with right language-dominance.

The study by Wibawa et al. (2019) shows that patients with anosognosia show more impairments of executive functioning which seemed associated with the degree of unawareness of their deficits. Wibawa et al used several measures including Symbol Digit Modality (SDMT), Stroop Interference, and Animal Verbal Fluency to measure the executive functioning in these patients (Wibawa et al., 2019).

Split-brain patients, whose hemispheres have been separated by cutting the bridging corpus callosum, show that hemispheres have independent awareness (Pinto et al., 2017). Indeed, during a Wada test the patient remains responsive and thus seems clinically aware. The current study will investigate how often a patient, a few minutes after the Wada injection, is not aware of an inability during the test and if this anosognosia can be profiled. We expect that anosognosia will occur when the non-language-dominant hemisphere is anesthetized and the patient has a pre-existing deficit in executive functioning. Because all Wada patients have undergone neuropsychological testing, we have access to these parameters. In addition to testing this hypothesis, explorative research will also be conducted to see if there are multiple remarkable observations to form new hypotheses in the future.

Methods

Data

Study data consisted of video recordings of the Wada tests performed in the University Medical Center Utrecht, and patient data as recorded in the electronic hospital files (Healthcare

Information X-change, HiX). This retrospective study included all adult patients who underwent a Wada test with methohexital between April 2015 and August 2019. Their demographic, neuropsychological and epilepsy data were retrieved from HiX. The video recordings have a total duration of approximately 14 hours.

Procedure

Before the Wada test, neuropsychological tests were performed on the patients to map cognitive functioning, in particular memory and language in the University Medical Center Utrecht or elsewhere. The patients were hospitalized one day before the Wada test at the Neurology/Neurosurgery Department. The procedure was explained and rehearsed with the patient on that day.

The Wada tests were monitored with an electroencephalogram (EEG) and videotaped. Before the injection, the neuropsychologist shows the patient three verbal and three figural stimuli. The patient is asked to remember these. 3 mg of methohexital is then injected into one internal carotid artery, while the patient holds up both arms and counts. After injection, a contralateral paresis of the arm is noted and ipsilateral EEG slowing reported by the neurologist. During the first few minutes after injection, language and memory is tested. In case of a second Wada test different memory items are used. The stimuli are shown on an iPad by the neuropsychologist who is standing on the side of the patient that is not in the patient's potential blind field. The neuropsychologist usually starts by assessing language by object naming. She shows the patient four new figural stimuli that the patient has to name or the neuropsychologist will say aloud if the patient cannot speak. To test language comprehension, this may be followed by the token test in which the patient has to point to certain figures named by the neuropsychologist. After this, the neuropsychologist will test short-term memory. First, the patient has to imprint four new verbal stimuli. The patient is then asked to recall the stimuli presented before the injection, each by choosing one out of four alternatives. After this, usually when the EEG effect has subsided, tactile extinction is tested on the arms or hands, and anosognosia is assessed through an interview. Finally, ten minutes after injection the patient has to recall the stimuli presented shortly after injection, each by choosing one out of four alternatives. A patient may be forced to choose. After the Wada test, the patient will stay a few hours in the ward to check vital signs and proper hemostasis of the arterial puncture site. If no complications occur, the patient can return home.

The video recordings were retrospectively reviewed to determine presence of anosognosia. Attention was paid to what the patients told about the test and their awareness of

paralysis, vision and language a few minutes after the methohexital effect was gone. Did they know that one arm fell or that they had problems with speech or language? These conversations about the awareness have been transcribed. These conversations were held to check whether patients could remember everything. It could be derived from the conversation if patients clearly stated if they had not noticed something. The intention was to assess the loss of awareness of one's functioning in the domains of paralysis, vision, and language. However, it turned out that this was not always clear for each domain. For that reason, it was decided to assess anosognosia in general. When a patient was unaware in any domain, this was assessed as anosognosia. In cases where patients did notice something odd, but could not describe what exactly, it was decided to denote the case as anosognosia. When there was doubt about the assessment of awareness, the video recording was also viewed together with Martine van Zandvoort to discuss how the case should be assessed.

While reviewing the recordings, attention was paid to which side was injected, how the patients scored on language and memory, and how long the EEG effect lasted, which was mentioned by the clinical neurophysiologist during the test and mentioned in the final EEG report in the electronic hospital files.

Analysis

Statistical analysis was performed using SPSS. A number of factors were tested to see if they are predictors of anosognosia. For this we defined a dichotomous variable where 0 stands for patients who show awareness of what happened and 1 for patients with symptoms of anosognosia. This was associated with several patient characteristics. Data not applicable got the code 777 and when it was unknown, 999.

Demographic data included sex, education according to Verhage coding, Dutch as first language and handedness. Because we included nominal and ordinal variables, non-parametric tests were used. To investigate whether the demographic data affects anosognosia, Fisher's Exact Tests were performed, only one Chi-Square Test was performed for the ordinal variable Education with seven levels.

The data set also contained neuropsychological data, viz. performance of short and long-term memory and executive functioning in general to see if anosognosia is related to these deficits in the brain. According to Wibawa et al. (2019) anosognosia is associated with poorer executive function and the *dissociable interactions and conscious experience model* (Agnew and Morris, 1998, Figure 1) shows that memory comes in when updating the representation of the current functions. We divided the variables “Memory” and “Executive functions” into

whether there were indications of disorders, with 0 for no, 1 for mild disorder and 2 for disorder. It was also taken into account whether the patient had a psychiatric history. Such a history may be related to anosogonosia, like depression and anxiety (Kalbe et al., 2005). The variable "Psychiatric history" had the conditions 0 for none, 1 for yes, longer than a year ago and 2 for yes, shorter than a year ago. These are ordinal variables. To investigate whether the neuropsychological data associate with anosognosia, Chi-Square Tests were performed.

Epilepsy variables were also examined. This include the variable "Age of onset", which looks at whether patients have epilepsy at an early age or not to see if brain development is involved. This variable is divided into the conditions younger and older than 18 years. In addition, the scale variable "Seizure Frequency" (seizures per month over the last year) to investigate whether the amount of seizures matter. Also, the nominal variable "Focus location" is included with the conditions 1 for temporal lobe and 2 for extratemporal and “Focus lateralization” being either right or left to see if it matters where the epilepsy focus is in the brain. Presence of impaired awareness during seizures was also scored. Will there be a difference between people who experience a decrease in awareness during epileptic seizures and those who do not have this? People with a decrease in awareness will be less scared of this, it is more difficult for people who have never experienced this before. For the nominal variables a Fisher’s Exact Test was performed and for the scale variable Logistic Regression.

Also, variables from the Wada test itself were considered. These are nominal variables. One variable was “Hemisphere injected”. The variable "Dominant" was about which hemisphere showed critical for language based on the Wada test. With this variable, the condition was 1 for the right, 2 for the left and, 3 for bilateral. These variables have been included to see whether lateralization plays a role. “Dominant injected” is about whether the injected hemisphere is shown critical for language. This variable is part of the hypothesis that expects anosognosia when injecting the non-dominant hemisphere. The scale variable "Duration" is about how many seconds the effect was seen on the EEG. The duration of the injection may have an effect on the processes in the *dissociable interactions and conscious experience model* (Agnew and Morris, 1998, Figure 1). We also looked at what the patients scored on language and memory tests during the Wada-tests to see if this functioning is related to anosognosia. Attention will have been paid to these tests which will require them to enter the episodic memory. These are scale variables with a score of 0 to 100 percent. The first test with the Wada Test is object naming. The variable about this is called "Language". During the effect of the methohexital, the patients were shown verbal and figural stimuli. Patients were asked to remember these for recall after the Wada procedure. The scale variables "Memory verbal" and

"Memory non-verbal" follow from this imprinting. For the nominal variables, a Fisher's Exact Test was performed, except for the variable Dominant, where a Chi-Square test is used. For the scale variables, a Logistic Regression was performed.

Finally, we tested the hypothesis that anosognosia will occur when the non-language dominant hemisphere is anesthetized and the patient is deficient in executive functions, which is about two independent variables. For this, we created a new variable by linking these two independent variables into the label "Non-dominant injection & deficit in executive functioning". To see if this hypothesis can be assumed, Fisher's Exact Test was performed.

Results

A total of 34 epilepsy patients participated in this study, 20 women and 14 men. 6 patients showed right-sided dominance and 1 patient bilateral dominance for language. A few underwent bilateral Wada procedures so that 52 Wada tests were included in this study. 17 Wada tests were not assessable on awareness, because it was not properly tested, or when the video or sound recording was missing. These were entered as missing values. 25 patients could be assessed. Of the 35 Wada tests that remained, 17 right hemispheres were injected and 18 left hemispheres.

To answer the question of how often patients, are not aware of their inability during the active phase of the Wada test, video recordings were reviewed. In 24 of 35 Wada tests patients were unaware of deficits and showed anosognosia. For example, they did not know that their arm had dropped or that they were unable to speak properly. This amounts to symptoms of anosognosia in 70% of cases.

We wanted to explore where such an anosognosia might depend on. Only a trend was found with Fisher's Exact Test for sex ($p = .069$, 2-sided) in which men are relatively less aware than women, see Figure 2. There was no significant result found for the presumed predictive variables, see Table 1.

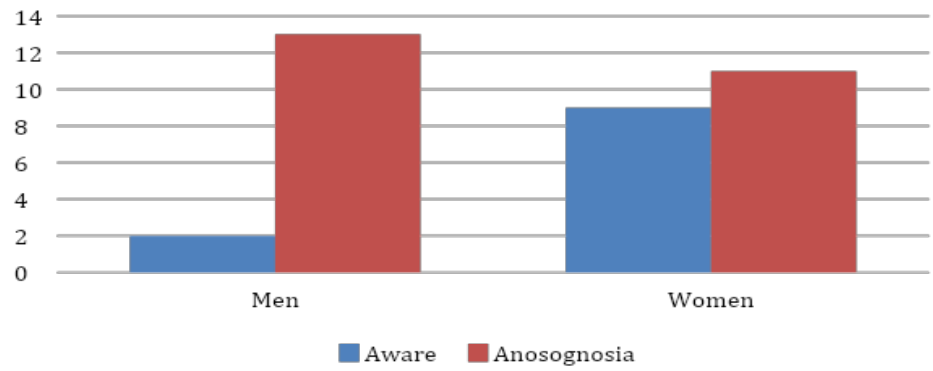


Figure 2. The effect of sex on Anosognosia

Table 1

The non-significant associations between the presumed predictive variables and the occurrence of anosognosia

Independent variable	Test	*Sig.*	*χ2*	*OR*	*95% CI*
Demographic					
Sex	Fisher Exact	.069			
Dutch as first language	Fisher Exact	1.000			
Handedness	Fisher Exact	.652			
Education	Chi-Square	.357	4.638		
Neuropsychological					
Memory	Chi-Square	.351	2.475		
Executive functioning	Chi-Square	.643	1.197		
Psychiatric history	Chi-Square	.422	1.403		
Epilepsy					
Aware Seizures	Fisher Exact	1.000			
Age at onset	Fisher Exact	.289			
Focus Location	Fisher Exact	1.000			
Focus Lateralization	Fisher Exact	.709			
Frequency seizures	Logistic Regression	.668		1.002	[.994, 1.009]
Wada test					
Hemisphere injected	Fisher Exact	1.000			
Dominant	Fisher Exact	.608			
Dominant Injected	Fisher Exact	1.000			
Duration	Logistic Regression	.505		1.008	[.984, 1.033]
Memory verbal	Logistic Regression	.135		1.017	[.995, 1.039]
Memory non-verbal	Logistic Regression	.584		1.007	[.983, 1.031]
Language	Logistic Regression	.671		1.003	[.989, 1.018]

Note. p<.05

Finally, the hypothesis is as follows anosognosia occurs when the non-language dominant hemisphere is anesthetized and the patient is deficient in executive functions. To test the null hypothesis, a Fisher's Exact Test was performed with the variables "Anosognosia" and "Non-dominant injection & disorder in executive functioning". This variable was also not significant (p = 1.000, 2-sided), see Table 2 for the 2x2 table.

Table 2
The Crosstabulation variables "Anosognosia" & "Non-dominant injection & disorder in executive functions"

	Non-dominant & EF disorder	Not non-dominant EF & disorder	Missing	Total
Aware	4	7	0	11
Anosognosia	8	15	1	24
Total	12	22	1	35

Discussion

We asked ourselves what makes a patient presents from anosognosia during a Wada test. We expected that anosognosia would occur when the non-language-dominant hemisphere is anesthetized and the patient is already deficient on executive functioning, based on Meador et al. (2000) and Wibawa et al. (2019). We could not confirm their findings.

Moreover, we could not find an association between a range of presumed predictive variables and the occurrence of anosognosia. The demographic, neuropsychological, epilepsy data and performance during the Wada test did not yield significant results. For example, it does not matter whether the epilepsy originates in the temporal lobe, which means that this location is not related or since when patients suffer from epilepsy, meaning it has nothing to do with the development of the brain. It also does not matter whether someone has problems with imprinting during the Wada test, which means that the patients have no problems with memory storage. This is also what we saw while watching the video recordings. There were people where the imprinting of verbal and figurative stimuli went well but did not realize that they could not speak and/or that the arm fell. Only a trend for male sex is found.

The lack of significant results can be attributed to limitations in the study. To start, the contradictory result about the association of executive functioning and anosognosia may be due to the umbrella term *executive functions* encompassing a broad spectrum of different cognitive processes in the literature and the use of various measurements. Moreover, this study included a small number of Wada tests. An increase in sample size may increase the power of the test which may result in drawing more firm conclusions. For future studies, it may be interesting to see whether or not the trend towards male depends on the number of Wada tests and whether other variables are associated with occurrence of anosognosia.

In addition, assessing anosognosia was difficult for several reasons. Anosognosia seems to occur in most cases during the Wada test when assessed by interview. Not questioning

systematically may lead to an underestimation of anosognosia, because patients do not always start about all induced deficits themselves. For example, it may be that someone has realized that he or she had problems with language, but not with control over one arm. In this study, insufficient data was available because not all domains of motor control, vision, speech and language were systematically checked. For this reason, it was decided to assess anosognosia in general. Also, patients know what is going to happen, because they have been prepared for this the day before. So they should know before the test that one arm will drop after injection. This makes it all the more remarkable that most patients are unaware of this. Patients may become aware of the fact that they missed something and may fill in this lost information themselves. This can be seen in the following case after the Wada test, which has been assessed as anosognosia:

N= Neuropsychologist, P= Patient

N: "Have you noticed anything?"

P: "No actually not"

N: "Has your arm fallen?"

P: "Well I didn't really notice either"

N: "(…) What do you think, would it have fallen?"

P: "Yes, he did fall, I know that"

N: "Can you still remember that?"

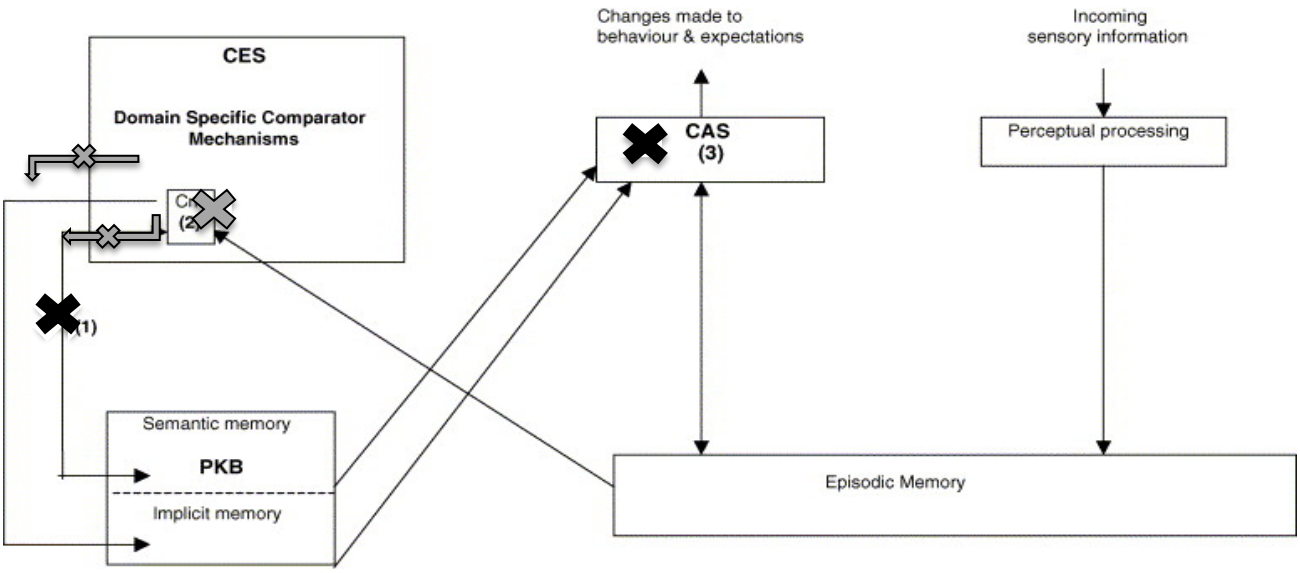
P: "Yes"

The question is whether this is about conscious experience, constructing memories or giving a socially desirable answer. Probably more patients will not have been aware of their impairments during the Wada test than was shown in this study, resulting in an underestimation of the actual amount of anosognosia occurrences.

Besides the fact that anosognosia is underestimated by not systematically checking all domains and filling in lost information, another limitation is the definition of anosognosia. Hemianopia prevents a patient from seeing the contralateral arm drop. Also, hemianesthesia may prevent proper somatosensory experience of the drop (Meador, Loring, Feinberg & Nichols, 2000), making it not very unusual for patients not to notice their deficits during the Wada. If no attention is paid to the deficit, it cannot be included in the system of the *dissociable interactions and conscious experience model* (Agnew and Morris, 1998, Figure 1). For this reason, it is questionable whether an unawareness of a falling the arm can be defined as anosognosia. It has been assessed as anosognosia in this study, which may lead to an overestimation that is likely to be even more frequent than the underestimate.

Conclusion and further research

Anosognosia is an interesting, high-order cortical integration failure that may interestingly depend on hemispheric failure. We expected that anosognosia would occur when the non-language-dominant hemisphere is anesthetized and the patient has a deficit of executive functioning, but this was not the case. We found no factors associated with occurrence of anosognosia. Only a trend for male sex is found. This was an unexpected result. Recent previous studies indicate that sex is not related to measures of anosognosia in Alzheimer's patients (Verhülsdonk et al., 2017; Antoine et al., 2019), but there has been previous evidence that sex may have an impact on anosognosia (Migliorelli et al., 1995). A possible cause to explain the trend that has been found, could be the motivation for refusing to recognize the disease as a way to deal with stress. In this way, anosognosia is seen as a defense mechanism in which disturbing symptoms are blocked from awareness (Marcel, Tegnér and Nimmo-Smith, 2004). This degree of motivation differs for sex and the task. It is possible that men overestimate a certain ability more often than women (Croson & Gneezy, 2009; Hubble & Zhao, 2016; Marcel, Tegnér and Nimmo-Smith, 2004;). This study gives reason to test whether a difference in sex is found when using a different data set of Wada tests.



Note. **(1)** = Deficit in the pathway between the Cm and semantic memory (Mnemonic anosognosia); **(2)** = A deficit in the Cm with the result that no information is sent to the implicit and semantic memory (Executive anosognosia); **(3)** = An impairment of the CAS (Primary anosognosia); **CES** = Central Executive System; **Cm** = Comparator mechanisms; **PKB** = Personal knowledge base; **CAS** = Conscious awareness system.

Figure 3. Impairments in the dissociable interactions and conscious experience model that cause anosognosia.

According to the *dissociable interactions and conscious experience model* (Agnew and Morris, 1998, Figure 1), anosognosia occurs when there is an impairment in this model. The current question is where it goes wrong when someone is unaware of the deficits during the injection of methohexital. This is interesting to find out in a follow-up study. When the problem lies in updating the PKB, the patients are unable to create an enduring awareness of their performance, but they show insight during the task (Ansell & Bucks, 2006). In the future, neuropsychologists could ask about the performance during the Wada test to see if the problem lies in the pathway between the Cm and the semantic memory (Figure 3, (1)). When the deficit is in the Cm, the patient cannot compare his performance to his PKB, leading to a lack of awareness of the deficit. In this case, no information is sent from the Cm to implicit memory, so there is no implicit learning (Figure 3, (2)). Only with this deficit the patient will not show behavioral changes (Ansell & Bucks, 2006). This deficit is difficult to investigate during a Wada test because implicit learning is likely to take longer than the duration of the injection. Research will be conducted into a task performed several times during Wada to see if the patient is adjusting to his or her performance. It will be necessary to investigate how long it will take to show the implicit changes in behavioral responses. Impairment of the CAS will result in unawareness of the state of functioning in all domains (Figure 3, (3)). But implicit learning is retained. The mismatch between the performance information and the contents of the PKB can influence behavior or mood, without explicit awareness of the deficits (Ansell & Bucks, 2006). To investigate whether anosognosia is caused by an impairment of the CAS, multiple domains will have to be systematically checked.

In future studies, we recommend to find out the impairment of the system (Agnew and Morris, 1998, Figure 1) and to consistently explore the domains motor function, vision, speech and language in a study with multiple data. Since it is not uncommon for the patient not to notice that the arm is falling, it is important to build in cues for the arm during the Wada test, in order to make someone think about his or her arm. This way, it can invade the system (Agnew and Morris, 1998, Figure 1) via the episodic memory and the patient can become aware of it if there is no anosognosia. In order not to have any problem with the definition of anosognosia, it is interesting to investigate what happens when only language anosognosia is considered. This was not possible in this study due to insufficient data. There were patients with language anosognosia, such as in the case below where the neuroposychologist tells the patient that he was unable to speak:

N= Neuropsychologist, P= Patient

N: You also couldn't speak.

P: I couldn't speak?

N: You don't remember?

P: No.

N: You could remember pictures, but everything that has to do with language is of no use to the other brain.

Language deficit which is being tested cannot escape attention like falling the arm and will be noticed by the system of the *dissociable interactions and conscious experience model* (Agnew and Morris, 1998, Figure 1). This makes it remarkable that a number of patients are unaware of this. It may play a role that the test is stressful and lasts a very short time with full recovery. Unlike the research in Alzheimer's disease which reveal that most people are not aware of their persistent cognitive impairment or illness. An explanation can be that the injection during the Wada test is too short to compare the performances with the existing information about the person's current function in the PKB or / and to update this so they don't become aware of it (Ansell & Bucks, 2006; Morris & Mograbi, 2013). That is why we are curious whether the use of another longer-acting drug will produce a different result.

References

Agnew, S. K., & Morris, R. G. (1998). The heterogeneity of anosognosia for memory impairment in Alzheimer's disease: A review of the literature and a proposed model. Aging and Mental Health, 2, 9–15.

Ansell, E. L., & Bucks, R. S. (2006). Mnemonic anosognosia in Alzheimer's disease: A test of Agnew and Morris (1998). *Neuropsychologia*, *44*(7), 1095-1102.

Antoine, N., Bahri, M. A., Bastin, C., Collette, F., Phillips, C., Balteau, E., ... & Salmon, E. (2019). Anosognosia and default mode subnetwork dysfunction in Alzheimer's disease. *Human brain mapping*, *40*(18), 5330-5340.

Blackmon, J. (2016). Hemispherectomies and Independently Conscious Brain Regions. *Details Journal of Cognition and Neuroethics (ISSN: 2166-5087). January, 2016*, *3*(4), 1-26.

Bremm, F. J., Grewe, P., Bien, C. G., & Hendriks, M. P. (2019). Pre-en postoperatief verbaal geheugen en executief functioneren bij frontaal- en temporaalkwabepilepsie. *Neuropraxis*, *23*(3), 53-62.

Chang, E. F., Breshears, J. D., Raygor, K. P., Lau, D., Molinaro, A. M., & Berger, M. S. (2017). Stereotactic probability and variability of speech arrest and anomia sites during stimulation mapping of the language dominant hemisphere. *Journal of neurosurgery*, *126*(1), 114-121.

Cocchini, G., Beschin, N., & Della Sala, S. (2018). Unawareness for motor impairment and distorted perception of task difficulty. *Journal of the International Neuropsychological Society*, *24*(1), 45-56.

Croson, R., & Gneezy, U. (2009). Gender differences in preferences. *Journal of Economic literature*, *47*(2), 448-74.

Danckert, J., & Ferber, S. (2006). Revisiting unilateral neglect. *Neuropsychologia*, *44*(6), 987-1006.

De Witte, E., Satoer, D., Visch-Brink, E., & Mariën, P. (2016). Taaltests voor, tijdens en na wakkere hersenchirurgie: de rol van DuLIP. *Neuropraxis*, *20*(3), 83-90.

Flöel, A., Buyx, A., Breitenstein, C., Lohmann, H., & Knecht, S. (2005). Hemispheric lateralization of spatial attention in right-and left-hemispheric language dominance. *Behavioural brain research*, *158*(2), 269-275.

Grote, A., Witt, J. A., Surges, R., von Lehe, M., Pieper, M., Elger, C. E., ... & Delev, D. (2016). A second chance—reoperation in patients with failed surgery for intractable epilepsy: long-term outcome, neuropsychology and complications. *J Neurol Neurosurg Psychiatry*, *87*(4), 379-385.

Hubble, C., & Zhao, J. (2016). Gender differences in marathon pacing and performance prediction. *Journal of Sports Analytics*, *2*(1), 19-36.

Kalbe, E., Salmon, E., Perani, D., Holthoff, V., Sorbi, S., Elsner, A., ... & Luedecke, S. (2005). Anosognosia in very mild Alzheimer's disease but not in mild cognitive impairment. Dementia and geriatric cognitive disorders, 19(5-6), 349-356.

Kho, K. H., Leijten, F. S., Rutten, G. J., Vermeulen, J., Van Rijen, P., & Ramsey, N. F. (2005). Discrepant findings for Wada test and functional magnetic resonance imaging with regard to language function: use of electrocortical stimulation mapping to confirm results: case report. *Journal of neurosurgery*, *102*(1), 169-173.

Kundu, B., Rolston, J. D., & Grandhi, R. (2019). Mapping language dominance through the lens of the Wada test. *Neurosurgical focus*, *47*(3), 1-7.

Marcel, A.J., Tegnér, R. and Nimmo-Smith, I. (2004). Anosognosia for plegia: Specificity, extension, partiality and disunity of bodily unawareness. Cortex, 40, 19- 40.

Meador, K. J., Loring, D. W., Feinberg, T. E., Lee, G. P., & Nichols, M. E. (2000). Anosognosia and asomatognosia during intracarotid amobarbital inactivation. *Neurology*, *55*(6), 816-820.

Migliorelli R, Tesón A, Sabe L, et al. 1995. Anosognosia in Alzheimer's disease: a study of associated factors. J Neuropsychiatry Clin Neurosci 7(3): 338–344.

Moro, V., Pernigo, S., Tsakiris, M., Avesani, R., Edelstyn, N. M., Jenkinson, P. M., & Fotopoulou, A. (2016). Motor versus body awareness: voxel-based lesion analysis in anosognosia for hemiplegia and somatoparaphrenia following right hemisphere stroke. *Cortex*, *83*, 62-77.

Morris, R. G., & Mograbi, D. C. (2013). Anosognosia, autobiographical memory and self knowledge in Alzheimer's disease. *Cortex*, *49*(6), 1553-1565.

Moshé, S. L., Perucca, E., Ryvlin, P., & Tomson, T. (2015). Epilepsy: new advances. *The Lancet*, *385*(9971), 884-898.

Pinto, Y., Neville, D. A., Otten, M., Corballis, P. M., Lamme, V. A., De Haan, E. H., ... & Fabri, M. (2017). Split brain: divided perception but undivided consciousness. *Brain*, *140*(5), 1231-1237.

Szantroch, M., Bala, A., Rysz, A., Żyłkowski, J., & Marchel, A. (2019). Experience of adverse events with cerebral propofol testing in patients with drug resistant epilepsy. *Scientific reports*, *9*(1), 592-597.

Tu, B., Assassi, N., Bazil, C. W., Hamberger, M. J., & Hirsch, L. J. (2015). Quantitative EEG is an objective, sensitive and reliable indicator of transient anesthetic effects during Wada tests. *Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society*, *32*(2), 152-158.

Van Zandvoort, M., Ruis, C., & Hendriks, M. (2016). Wakkere hersenoperaties: de klinisch-neuropsychologisch aspecten. *Neuropraxis*, *20*(3), 91-95.

Verhülsdonk, S., Lange-Asschenfeldt, C., Höft, B., Schwender, H., Supprian, T., Hellen, F., & Kalbe, E. (2017). Repressive coping does not contribute to anosognosia in first-diagnosis patients with Alzheimer disease. *Alzheimer Disease & Associated Disorders*, *31*(3), 249-255.

Wibawa, P., Zombor, R., Dragovic, M., Hayhow, B., Lee, J., Panegyres, P. K., ... & Starkstein, S. E. (2020). Anosognosia Is Associated With Greater Caregiver Burden and Poorer Executive Function in Huntington Disease. *Journal of Geriatric Psychiatry and Neurology*, *33*(1), 52-58.

Woermann, F. G., Jokeit, H., Luerding, R., Freitag, H., Schulz, R., Guertler, S., ... & Ebner, A. (2003). Language lateralization by Wada test and fMRI in 100 patients with epilepsy. *Neurology*, *61*(5), 699-701.

Zago, L., Petit, L., Jobard, G., Hay, J., Mazoyer, B., Tzourio-Mazoyer, N., ... & Mellet, E. (2017). Pseudoneglect in line bisection judgement is associated with a modulation of right hemispheric spatial attention dominance in right-handers. *Neuropsychologia*, *94*, 75-83.