Functional Movement Disorders: Attention, Agency and Beliefs

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Declaration

I, Anne-Catherine Huys, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Personal contribution statement

I led the development of all study designs, programmed all experiments, created the experimental setups, contacted all participants for recruitment, collected all the data, wrote all the scripts for data analysis except for the linear mixed effects model presented in annexe A 9.1, and analysed and interpreted all the data. Furthermore, I wrote the ethics application in addition to the amendments. Finally, I wrote and obtained two grants for this study (Guarantors of Brain Entry Fellowship and Association of British Neurologist Clinical Research Training Fellowship). Throughout this process, I received help and guidance from my supervisors.

Abstract

This work centers around three aspects of the likely pathophysiology of functional movement disorders: attention, agency and beliefs.

The most characteristic, yet intriguing feature of functional neurological disorders is that symptoms typically manifest with attention and improve or disappear with distraction. In an attempt to elucidate what the abnormal attentional focus is, it was manipulated onto different aspects of a reaching movement. Attention in functional tremor seems to be misdirected to the ongoing visual feedback of the movement and this seems to partly contribute to the symptoms. Furthermore, the attention network test indicates that the executive network is impaired.

Functional movement disorders share many characteristics with voluntary movements, raising the question whether it is in fact the sense of agency that is the primary abnormality in this disorder. The sense of agency was measured in the context of different attentional foci and with subliminal and supraliminal priming. No abnormalities were detected, although this might have been linked to methodological difficulties.

Subliminal priming confirmed that implicit motor control is normal in patients with functional movement disorders.

Functional neurological disorders sometimes appear to follow lay beliefs. In order to evaluate if their beliefs about their symptoms are abnormal, functional tremor patients' perception of their tremor was evaluated in real time and in retrospect. It was found to be accurate and not dissimilar to organic tremor patients' perception. Attempting to change their beliefs, by modifying the visual feedback they were given did not have any lasting effect on functional nor organic tremor.

Dramatic placebo effects are occasionally observed in functional neurological disorders, having led to the conclusion that patients with these disorders are suggestible. A classic placebo analgesia experiment did not show stronger placebo responses in patients with functional neurological disorders than healthy controls, suggesting that the notion of suggestibility is mistaken.

Impact statement

Functional neurological disorders are very common. They are the second most common diagnosis in new patients attending neurology clinics. The quality of life of patients afflicted by these disorders is poor and they generally carry a poor prognosis. In addition to the impact on the affected individuals and their families, the associated costs to society are huge. Yet, these disorders are amenable to treatment and can at times recover completely. This highlights the immense potential there is in the treatment of these conditions; the immense impact we could have on individuals, their families and, in view of the monetary costs, on society as a whole. The reality is, however, that these disorders are still poorly understood, and that treatment options are often limited.

The primary aim of this work is to further the understanding of the pathophysiology of functional movement disorders in order to improve their treatments and ultimately help our patients. How the findings can be incorporated into a larger model of functional movement disorders and their direct treatment implications is discussed in detail in the final chapter.

The survey on the use of placebo treatments in medicine is an opportunity for patients to make their opinion heard. Taking this into account is central to guide clinical practice.

Since it is argued that healthy individuals can at times experience symptoms that are analogous to functional symptoms, the treatment approaches used for functional disorders can also be applied to healthy individuals to prepare them for certain situations.

A further aspect is that there is still a lot of stigma and misconceptions surrounding these conditions. When affected patients perceive such negative attitudes in healthcare professionals the results can be detrimental to their care. They might not feel believed but dismissed and not listened to. As a consequence, they are unlikely to believe their diagnosis and ultimately might even lose trust in the medical profession. Part of the reason these negative attitudes persist is probably due to the fact that these disorders are poorly understood, might at times appear contradictory, illogical, almost mysterious. Hence, they might be perceived as unreal. Not knowing how to manage and treat, or even how to explain these disorders, might make doctors feel uncomfortable, which can ultimately manifest itself as a dislike of these disorders.

This work will hopefully help remove some of these negative attitudes, by having been able to demystify these disorders to some degree by clarifying some aspects of their pathophysiology, by showing the links to common experiences in healthy individuals and by directly testing and rectifying the misconception of suggestibility.

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Abbreviations

FND	Functional Neurological Disorder
FMD	Functional Movement Disorder
HC	Healthy Control
OC	Organic Control (patient with the equivalent organic disorder)
OT	Organic Tremor

Acknowledgements

Chapter 1 Introduction

1.1 Functional neurological disorders (FND)

Functional disorders have seen many name changes over the years, reflecting the times' understanding and often misunderstanding of these disorders: In the not so distant past, functional disorders were called "hysteria", originating from the Greek υστερία for uterus. It was originally thought that the symptoms were provoked by the uterus wandering around the woman's body.

According to Sigmund Freud and Josef Breuer, who coined the term conversion disorders, psychological problems (typically repressed ones) are "converted" into physical symptoms (Breuer and Freud 1895). For the same implied reason, functional disorders are also known as "psychogenic" or "psychosomatic". In the Diagnostic and Statistical Manual of Mental disorders (DSM) 5 it is termed "conversion disorder (functional neurological symptom disorder)" and is part of the broader category "Somatic Symptom and related disorders" (American Psychiatric Association 2013). While psychiatrist mainly call it conversion disorder, neurologists until recently used to apply the term psychogenic. Psychological factors, in particular psychological trauma, are risk factors, but they are absent in a large proportion of patients (see below). Just as the term hysteria is offensive, the term psychogenic can be so too. It is frequently misunderstood by patients as meaning that "it is all in their mind", that the symptoms are imagined, or a consequence of their psychological weakness. The term psychogenic is thus alienating and the term functional is more appropriate and acceptable to patients (Edwards, Stone, and Lang 2014; Stone et al. 2002). Similarly, the term "medically unexplained" is unhelpful as it implies that nothing is known about the disorder and that the correct diagnosis has yet to be found.

Since functional disorders are a product of the brain, just as any other neurological disorder that is not due to spinal or peripheral nervous system dysfunction, the term "non-organic" is misleading and so is the term "organic" for all non-functional disorders. Nevertheless, for lack of a better term, I will use the term "organic" for disorders that are not of functional nature.

Functional neurological symptoms at first sight might appear like standard neurological disorders, such as stroke, epilepsy, multiple sclerosis or others, but characteristic features distinguish them.

Incongruence: The symptoms are often incongruent in time or place. They might change location within the body or fluctuate in a manner that does not occur in organic disorders. In functional paralysis for example, the patient is not able to voluntarily move a limb but has normal strength when moving the same limb in a more automatic way; gesturing with their hands while talking for example or moving their leg when readjusting their posture. Another example is functional blindness in which patients are effectively blind in one eye. When rapidly changing lenses are placed in front of their eyes, they cannot tell which eye is covered and normal visual acuity can be demonstrated. Another interesting example is foreign accent syndrome, in which the affected

person develops a foreign accent with the associated grammatical errors a person of that origin would make. Once again, when their speech is more automatic, such as when saying “No thank you.” “See you soon” or similar semi-automatic utterances, their speech is normal.

Symptoms sometimes seem to follow lay people´s beliefs and are incongruent with what is currently known about brain function. The just mentioned foreign accent syndrome, in which not only the accent is affected, but also grammar is one example. Another one is tubular vision, in which, regardless of how close or far a person is, they can only see the same diameter, as if they were looking through a tunnel; something that clearly defies the laws of optics. It is not unusual for organic symptoms to fluctuate, but functional neurological disorders do so to a much larger extent. It is also not just the severity that might fluctuate, but the actual symptoms can change and vary to a degree that is not be seen in organic disorders. In a few select cases, non-physiological manoeuvres, such as for example pressing a certain spot on the body can transiently stop the symptom.

Distractibility: The most characteristic feature is that functional symptoms typically manifest when the patient pays attention to them and improve or even disappear with distraction. As such symptoms can vary from one second to the next and can be markedly altered by attention. The way functional tremor is diagnosed, for example, is by observing the patient’s tremor momentarily disappear while the patient is distracted by another task or action.

Suggestibility: The fact that symptoms are rather suggestible can be partly explained by the fact that drawing attention to them accentuates them. Another characteristic feature is that functional disorders sometimes show dramatic placebo responses. Due to the time needed to be absorbed and affect synaptic transmission, the biological effect of botulinum toxin injections only starts to be seen 2-4 days after the injection. In functional fixed dystonia, however, administering a minute dose of botulinum toxin can lead to the disappearance of the dystonia seconds after the injection (Edwards, Bhatia, and Cordivari 2011). For a more in-depth discussion of the placebo effect in FND, see 1.2.3.1

Interference by voluntary movements: Functional movement disorders have the additional feature of interfering with, or rather being interfered by voluntary movements. Entrainment describes the phenomenon of a functional tremor taking on the frequency of a voluntary movement, e.g. finger tapping with the contralateral hand. Some patients even describe their movement disorder, typically a tremor, taking on the rhythm of a piece of music.

Given their fluctuating nature, the incongruences and the occasional dramatic placebo responses, it is clear that functional symptoms are due to a malfunctioning of the system and not due to a fixed structural, genetic or biochemical abnormality.

Triggers / risk factors: Functional disorders often have a sudden onset (Pareés et al. 2014). The onset is frequently preceded by a physical, often only minor, trauma or illness (Pareés et al. 2014; Stone et al. 2009). Functional neurological disorders are more common in young women in their thirties but men and people of any age, from childhood to old age, can be affected (Batla et al. 2013; Kirsch and Mink 2004). Illness exposure is a possible risk factor, since so-called "functional overlay", functional symptoms in addition to organic symptoms are not uncommon (Onofrj et al. 2011; Parees et al. 2013). However, contrary to previous impressions, FND is not more common in people working in healthcare (Perry et al. 2017).

The prevalence of psychological trauma and psychiatric comorbidity varies widely between studies. This is probably a reflection of the researchers' bias, since psychiatrist tend to see more patients with psychological traumas or psychiatric diagnoses, whereas neurologists tend to look after relatively more patients without such conditions. Thus, compared to organic disorders, certain papers quote higher rates of psychological traumas or psychiatric comorbidity, whereas other quote equal rates (Epstein et al. 2016; Feinstein et al. 2001; Gelauff et al. 2014; Kranick et al. 2011; Nicholson et al. 2016). In DSM-5, psychological stress or trauma is no longer an obligatory diagnostic criteria (American Psychiatric Association 2013). An additional factor to consider is whether certain psychiatric comorbidities such as anxiety or depression precede the FND or whether they are a reaction to it. It is undisputed that psychological trauma can be the trigger of a functional disorder, but it is not obligatory and thus not always relevant.

Symptoms: Functional disorders exist in every speciality. Functional blindness, pelvic pain syndrome, irritable bowel syndrome, atypical chest pain, shortness of breath, fibromyalgia are only some examples from the fields of ophthalmology, gynaecology, gastroenterology, cardiology and rheumatology. Even though the manifestations of these disorders are very different, given they frequently coexist, may change from one to another and seem to be changeable with attention as elucidated in the case of functional blindness, it is likely that the underlying mechanisms are similar.

The most common functional manifestation in neurology are non-epileptic attacks. While they might superficially seem like epileptic seizures, the electroencephalogram is normal during episodes and many additional features indicate a functional origin.

Functional *movement* disorders are movement disorders that are of a functional nature. Within movement disorders, functional tremor is the most frequent. Other examples, some of which have already been mentioned are functional paralysis, fixed dystonia, functional myoclonus, functional parkinsonism, functional gait disorders and functional tics.

Typically, the intensity of a given symptom initially rapidly progresses to maximum severity, and

then remains fairly static. Symptoms frequently change from one type to another over months or years or additional symptoms develop. As a consequence, most patients with functional disorders have more than one symptom. Associated fatigue is very common.

Prevalence: Somehow surprisingly, given the relative lack of interest in functional neurological disorders, they are the second most common diagnosis (16%) in new patients attending neurology outpatient clinics (Stone et al. 2010). Five to ten percent of patients seen in movement disorder clinics have a functional diagnosis and up to 50% of admissions to hospital with "status epilepticus" are in fact non-epileptic attack disorders (Stone 2009). Finally, as already mentioned, many patients with a clear organic neurological diagnosis have additional functional symptoms, so-called "functional overlay" (Parees et al. 2013; Stone et al. 2012).

Costs: The estimated costs of £17.5 billion for "medically unexplained symptoms" slightly surpassed the costs for dementia in the UK and were thought to account for approximately 10% of total NHS expenditure for the working-age population in 2008-2009 (Bermingham et al. 2010; Knapp and Prince 2007).

Quality of life & prognosis: Functional neurological disorders lead to as severe an impairment in quality of life as the equivalent organic diseases (Carson et al. 2011). Although spontaneous remissions can occur, functional symptoms typically recur, transform into another symptom or simply persist and overall they carry a poor prognosis (Gelauff et al. 2014, 2019; Stone et al. 2003). Contrary to frequent worries of clinicians, misdiagnosis is actually rare (Gelauff et al. 2019). The longer the duration of the disorder, the worse the prognosis, highlighting the importance of early diagnosis and management.

Treatment: Management depends on each individual patient´s symptoms, comorbidities and risk factors. In mild cases, giving the diagnosis and explaining it properly, is sometimes sufficient for the symptoms to improve. The impact of reassurance cannot be underestimated as anxious rumination about symptoms will inevitably lead to their worsening, and its cessation to their improvement.

There is no indication for drug therapy, unless there is a comorbidity, such as for example anxiety or depression. Functional neurological symptoms by themselves do not respond to medication. The exception is through possible placebo effects – but the use of deceptive placebo is marred with ethical issues. Discontinuing unnecessary medication and thereby avoiding its side-effects is therefore one aspect of treatment.

Specific psychological therapy is indicated in patients in whom psychiatric comorbidity, or previous traumatic experiences are thought to contribute to symptom generation. Cognitive

behavioural therapy on the other hand can be helpful for most patients. It helps to identify and address maladaptive coping strategies that typically develop. (Sharpe et al. 2011)

In the case of functional movement disorders, specialised physiotherapy, has been shown to be beneficial (Nielsen et al. 2015, 2017; Nielsen, Stone, and Edwards 2013). Standard physiotherapy, with focus on the impaired movement might worsen the symptoms. Instead, specialised physiotherapy focuses primarily on distraction techniques and on getting the movement to occur in an automatic manner. In some select patients, such as for example functional tremor patients who show entrainment, they can be taught how to entrain their tremor and gradually make it decrease in frequency until it is disappears entirely. This can also be done with the help of specialised devices (Espay et al. 2014).

Finally, more complex presentations might require a specialised multidisciplinary approach, which lead to relatively good outcome (Saifee et al. 2012). These combine physiotherapy, occupational therapy, cognitive behavioural therapy, neurological and psychiatric input.

1.2 Pathophysiology

The pathophysiology of functional neurological disorders is still poorly understood. Different aspects can be involved, particularly the limbic system, the attentional system, the sense of agency and beliefs.

Strong emotional triggers can certainly affect the motor system: the adrenergic fight fright and flight response increases muscular tension, which in turn can lead to tremor. The freeze response is probably an evolutionarily advantageous response to prevent detection by a predator, who tend to detect their prey based on movement. Similarly, not feeling pain while in the middle of a battle provides a clear survival advantage. Functional symptoms might in part be caused by these responses being expressed outside of their usual context. Indeed, functional imaging studies frequently show activation of the limbic system, which connects to the motor system via the striatum (Aybek et al. 2014; Mehta, Rowe, and Schrag 2013; Voon et al. 2010, 2011). According to the Freudian model, these findings are often interpreted as the limbic system driving abnormal movements.

The current work is focused on the pathophysiology outside of the limbic system, since many patients develop functional neurological disorders in the absence of any psychopathology or psychological trauma.

1.2.1 Attention

As detailed in 1.1 attention plays a crucial role in functional neurological disorders. Attention to the symptoms exacerbates them, and distraction leads to their improvement or even disappearance.

Defining attention as a single "thing" is impossible. Instead it is better viewed as a set of processes that allows us to ignore irrelevant information and use the brain's limited processing ability for the information that is most important in a given situation (Kastner 2014).

Two types of attention were classically distinguished (Posner 1980, Norman&Shallice 1986): "top-down" and "bottom-up". "Top-down" attention is also called "endogenous" because it involves conscious direction of attention and is thus "internally" generated. The focus of attention can be a location in space (focal attention), a particular feature, e.g. a colour (feature-based attention), an object (object-based attention) or other. "Bottom-up" attention on the other hand is called exogenous attention because it occurs automatically in response to an external stimulus. A flash of light in the peripheral visual field for example will automatically attract one's attention.

Attention was later divided into three networks: alerting, orienting and executive. The alerting network, as the name implies, leads to alertness and vigilance. It involves the neurotransmitter

noradrenaline and anatomically the reticular activating system in the brainstem and the right cerebral cortex. The orienting network allows to focus either on a location in space or a modality, i.e. a specific feature. It is formed by frontal and parietal regions and the neurotransmitter acetylcholine plays a crucial role in it. Finally, the executive network is involved in "top-down" control, in focal attention, and conflict resolution (withholding a response in favour of a less obvious response) and involves the medial frontal cortex / anterior cingulate cortex and parietal regions. (Fan et al. 2005; Posner and Petersen 1990)

Later, the orienting and executive networks were suggested to be further subdivided, leading to a total of five attention networks. The orienting network was subdivided into a more dorsal system including the interparietal sulcus and the frontal eye fields; and a more ventral system including the ventral frontal cortex and the temporoparietal junction (involved in switching location). The executive network was subdivided into a frontoparietal network (involved in task switching, initiation and adjustments), and into a cingulo-opercular network (involved in the maintenance of attention throughout a task). (Petersen and Posner 2012).

In the case of functional movement disorders, two main questions arise: Is attention abnormal in functional movement disorders or is it normal, but directed to the wrong aspect of the movement?

Attention is generally said to be normal in functional movement disorders and indeed functional neurological disorders in general with the exception of non-epileptic attack disorder (Heintz et al. 2013; Teodoro, Edwards, and Isaacs 2018). Yet, in the case of functional movement disorders in particular, relatively few studies have been performed to date.

In terms of a simple hierarchical model of motor control, it is clear that the key to successful movement is to spend one's cognitive resources on the intention level, the goal, and that the execution of the movement is delegated to low level, implicit, automatic circuits (figure 1A). When we use a fork to eat a cake for example we do not think about which joints or even muscles we need to move by how much, with which force or speed, we just focus on the desired end result, i.e. tasting the cake, and our motor system executes the movement automatically.

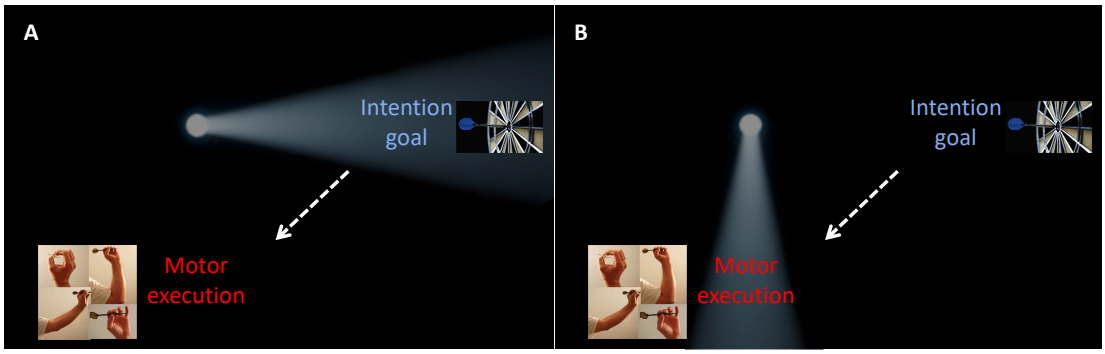


Figure 1: simple hierarchical model of motor control

A: In the case of dart throwing, after the learning phase, the attentional focus normally lies on the dartboard, the goal. B in functional movement disorders, the attentional focus is hypothesised to be misdirected to the mechanics of motor execution.

A hint that attention in functional movement disorders is misdirected comes from clinical observation: functional tremor patients look at their affected limb 66% of the time, twice as much as patients with organic tremor (Van Poppelen et al. 2011). We tend to look at what we are paying attention to so this points towards increased attention to the affected limb.

Numerous movement studies in healthy subjects, mostly in the context of sports, have shown that adopting an "internal, body- focused attention" impairs performance compared to adopting an "external, goal-focused attention"(Lohse, Sherwood, and Healy 2010; Wulf 2007; Zachry et al. 2005). The mechanism by which a misallocation of attention to the mechanics of motor execution is thought to lead to impaired movements is by disrupting the automatic motor processes, which are generally much better at fine motor control than conscious processes (Wulf 2007).

A frequent finding in functional imaging of functional movement disorders is an increased prefrontal cortical activation (Cojan et al. 2009; De Lange, Roelofs, and Toni 2007; Marshall et al. 1997). Interestingly, a study comparing genetic with functional dystonia detected the same prefrontal activation not only in the functional but also the organic patients (Schrag et al. 2013). These findings might be related to a study in healthy volunteers showing prefrontal and anterior cingulate cortex activity when subjects paid attention to the individual components of an automatic movement sequence (Jueptner et al. 1997). In other words, the increased prefrontal cortical activation commonly but not exclusively seen in functional movement disorders could be due to a misdirected attentional focus onto the mechanics of motor execution. As always, it remains an important question whether these findings represent causative, secondary or compensatory mechanisms (Mehta et al. 2013).

Can functional movement disorders be improved or even normalised for prolonged periods by a change in attentional focus? Conversely, can organic movement disorder patient´s abnormal movements be worsened, essentially rendered functional, by misdirected attention? Can even

healthy subjects be transitorily rendered functional by an abnormal focus of attention? What exactly is the abnormal focus of attention in functional movement disorders? All these questions remain unanswered but are of crucial importance for the understanding of functional movement disorders and ultimately their treatments.

Furthermore, could a misdirected focus of attention also be partly responsible for a decreased sense of agency?

1.2.2 Agency

Sense of agency is the sense of controlling one's own actions. In other words, it is the conscious experience that one has volitional or willed control over one's own actions, and that through these actions one can influence the environment (Wolpe and Rowe 2014). Agency is at the forefront of free will, as free will, the awareness that we chose to make movements is only possible if we feel in control of these movements, i.e. if we have a sense of agency over them.

The reasons for suspecting an abnormality of the sense of agency in functional movement disorders are manifold: The abnormal movements in functional movement disorders share many characteristics of voluntary movements. First, as mentioned above, the symptoms manifest with attention and mostly disappear with distraction. Second, other voluntary movements interfere with functional movement disorders, in the same way two voluntary movements interfere with each other. As an example, tapping at a certain frequency with the contralateral hand, leads to so called "entrainment"; the functional tremor in the affected hand takes on the contralateral hand's taping frequency (Schwingenschuh et al. 2011). Furthermore, certain functional movement disorders are preceded by a "Bereitschaftspotential" a readiness potential on electroencephalography, which is typically present in voluntary and absent in involuntary movements (Terada et al. 1995). Patients, however, clearly state that these abnormal movements are involuntary. While some might think that some patients labelled as "functional", might be malingering, the vast majority seem not to be (Pareés et al. 2012). Thus, the fact that patients report a clear lack of agency over these abnormal movements points towards a possible dysfunction in their subjective experience of action.

Agency can be measured by explicitly asking participants to give a rating of their sense of agency, on a scale of say 1 to 8. An implicit measure of the sense of agency is intentional binding: When an action is carried out in a voluntary fashion and followed by an effect (typically a button press, followed 250ms later by a tone), then the perceived timing of this voluntary action and its effect move closer together: they are "bound together" (Figure 2). This effect is called intentional binding, because it is only clearly present in voluntary (intentional) actions (Haggard, Clark, and Kalogeras 2002).

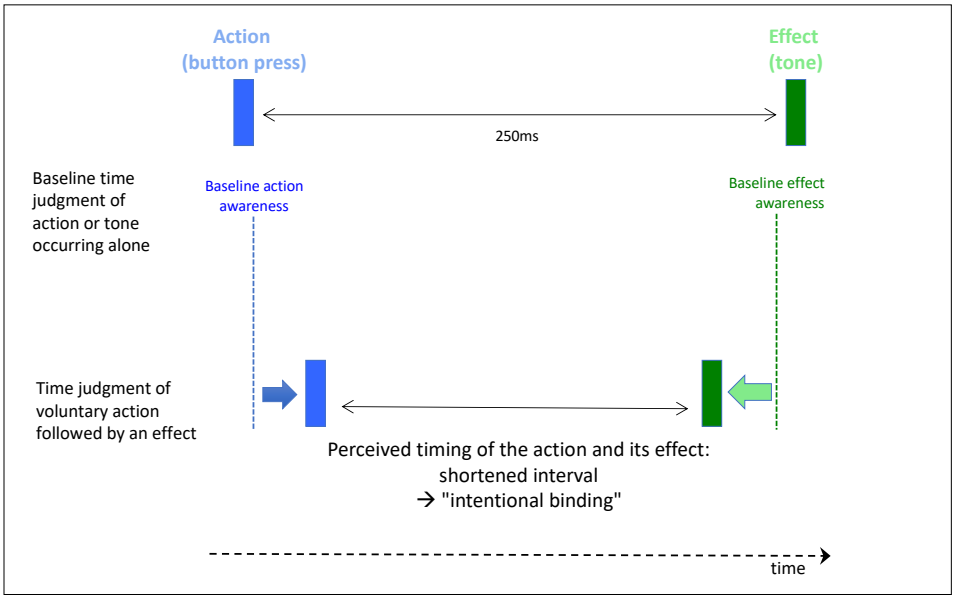


Figure 2: Intentional binding
Subjects press a button at a time of their own choosing and 250ms later a tone sounds. In baseline trials they judge the timing at which they press a button (without the button press being followed by a tone) and in separate baseline trials they judge the timing of a randomly appearing sound. These timing estimates are the baseline action and effect awareness. When asked to judge the timing of their own action (the button press) when it is followed 250ms later by a tone, they perceive their action to occur later, and the timing of the effect, the tone, to occur earlier. This temporal attraction in the perceived timing between a voluntary action and its effect is called intentional binding and is an implicit measure of the sense of agency.

Intentional binding is decreased in functional movement disorders (Kranick et al. 2013). This is somehow not surprising, given their lack of control over their abnormal movements. On the other hand, it is surprising, because the actions in the intentional binding tasks, the button press are *voluntary* actions. A likely interpretation is that they experience a decreased sense of agency even over simple voluntary actions.

In the Libet experiment (Libet et al. 1983) subjects are asked to press a button at a time of their choosing while watching a rapidly rotating clock hand. They are asked to indicate the position of the clock hand (and hence the timing) when they had the first awareness of intending to move. This time point is termed “W” for willing. In a different block they are asked to indicate the time at which they are aware of moving their finger “M”. “W” typically occurs 200ms prior to the onset of the finger EMG, “M” typically occurs 90ms prior to the EMG onset. The latter provides support for a feedforward, predictive model, such as the comparator model mentioned below.

Functional tremor patients show an abnormal pattern, in that their perceived time of willing the action and their perceived time of performing the action are not significantly different from each other. These findings indicate an impairment in the conscious experience of willing a voluntary movement (Edwards et al. 2011).

According to optimal motor control theory, when a motor command is generated by the brain a parallel, efference copy of this motor command is generated, leading to the prediction of the desired outcome. The "comparator" model for agency states that if this motor prediction matches the actual outcome of the movement, which is fed back by sensory circuits, then the outcome is perceived as self-generated, i.e. the person feels a sense of agency over that action. If there is a mismatch between the predicted and the actual outcome, then it is perceived as externally generated, i.e. there is a lack of agency over that action (Figure 3) (Blakemore, Wolpert, and Frith 2002).

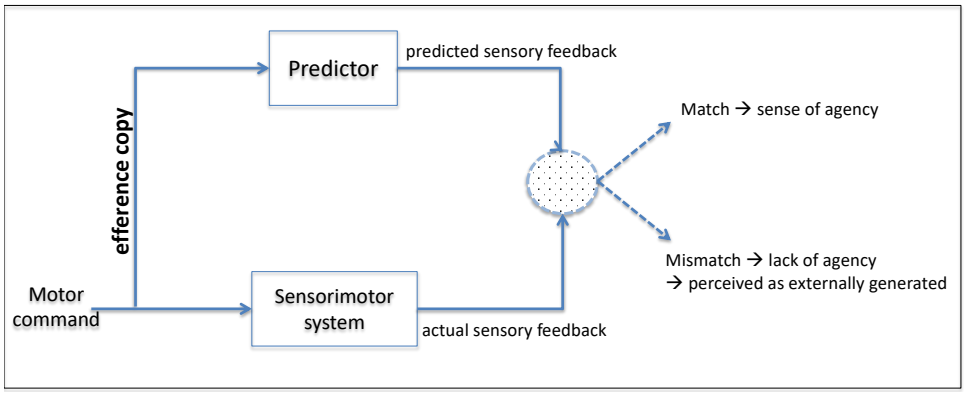


Figure 3: Simplified version of the comparator model

Could a misdirected focus of attention lead to a decreased sense of agency? There are several reasons why this might be the case. It might be because the movement is impaired, leading to a mismatch between the predicted and the actual outcome. Alternatively, focusing on the movement itself, rather than on the goal, might mean that the outcome, i.e. the goal, is not predicted properly, thus again leading to a mismatch.

It remains an open question as to whether the sense of agency per se is abnormal in FND or if it is only impaired in the context of voluntary actions.

Subliminal priming offers a way of influencing actions or decisions. A visual stimulus (the "prime") is shown for a very short period, and its processing interrupted "masked" by the presentation of another stimulus (the "mask") shortly after. The processing of the prime does thereby not reach consciousness, but it is nevertheless processed at a subliminal level and can therefore influence subsequent responses.

Comparing the sense of agency with subliminal as opposed to supraliminal priming gives the opportunity of investigating whether it is the sense of agency per se that is affected, or if it is only the sense of agency in the context of explicit movement control that is abnormal in FND.

1.2.3 Beliefs

Beliefs seem to play a pivotal role in functional neurological disorders.

Functional symptoms often reflect lay people's beliefs about brain function, which are in disagreement to what is known about the central nervous system. In addition to tubular vision and foreign accent syndrome mentioned in 1.1, other examples are sensory symptoms defying anatomical territories; a tremor that is being restrained spreading to an adjacent body part (somehow inappropriately termed "whack a mole sign" (Park, Maurer, and Hallett 2015); the triggering of symptoms by non-physiological manoeuvres, such as the appearance or disappearance of a functional movement disorder when pressing on a particular body part such as the shoulder or the umbilicus (Batla et al. 2013); or forgetting one's name in functional memory loss, something that is not seen until the very final stages of organic dementia.

In an elegant study, functional tremor patients reported 65% longer durations of tremor than simultaneous actigraphy recordings (compared to 28% in the organic group). They perceived their tremor to be present 84% of the waking day with actigraphy only recording 4% (Pareés et al. 2012). In addition, the tremor seemed to be more marked around the time patients with FND filled in their tremor diary. Thus, either attention to, or the expectation of their symptoms lead to their exacerbation.

Similarly, patients with functional motor symptoms subjectively rate their symptoms worse, than when they are asked to evaluate a simultaneously taken video recording (Ricciardi et al. 2015).

A strong belief in an abnormal movement might in fact lead to the prediction of that abnormal movement, with the brain merely executing the prediction. These notions are reminiscent of the nocebo effect or the concept of the self-fulfilling prophecy (Merton 1948).

Viewed in a Bayesian framework, the prior, the expectation or belief of having a symptom can bear more weight and can even override the actual sensory information that the symptom is in fact very mild, thus leading to the perception of a severe symptom. (Edwards et al. 2012)

Given the importance of beliefs, several questions arise:

> *Are beliefs normal in patients with FND?*
>
> *Are patients with FND more susceptible to manipulation of beliefs than patients with organic disorders?*
>
> *Can their beliefs be changed so as to improve their symptoms?*

The second question leads on to the placebo effect:

1.2.3.1 Placebo effect in FND

The placebo effect is the improvement of symptoms following the administration of an inactive substance or sham intervention.

Its **mechanisms** are slowly being unravelled. There is ample evidence that placebo treatments affect the neurotransmitters and brain regions generally affected by an equivalent active drug. A placebo administered for pain relief, affects the brain and even spinal cord regions involved in pain control and thus analgesia (Eippert, Bingel, et al. 2009; Eippert, Finsterbusch, et al. 2009; Petrovic et al. 2002; Wager, Scott, and Zubieta 2007). An antidepressant placebo on the other hand has an effect on similar brain regions as selective serotonin reuptake inhibitors (Mayberg et al. 2002). At an even more detailed level, placebo analgesia can be shown to affect the opioid system (Eippert, Bingel, et al. 2009; Levine, Gordon, and Fields 1978; Wager et al. 2007), the cannabinoid system (Benedetti et al. 2011), and in specific cases even the cyclooxygenase–prostaglandin pathway (Benedetti, Durando, and Vighetti 2014). An effective placebo given instead of a dopaminergic drug in Parkinson´s disease leads to endogenous dopamine release in the striatum (de la Fuente-Fernandez et al. 2001), and improves the abnormal firing pattern of the subthalamic nucleus, the substantia nigra pars reticulata, and motor thalamus, as recorded through implanted deep brain stimulation electrodes (Benedetti et al. 2004, 2009).

How this occurs is still unclear. Is it a top-down process, a form of reward, a learned response, or a combination of these? The involvement of the prefrontal cortex in placebo effects indicates a "top-down", high level mechanism, which is likely to influence downstream, disease specific mechanisms (Amanzio et al. 2013; Cavanna, Strigaro, and Monaco 2007; Eippert, Bingel, et al. 2009; Wager et al. 2007). Others postulate an involvement of the dopaminergic reward system, not only in motor placebo responses in Parkinson disease, but also in placebo analgesia (de la Fuente-Fernandez, Schulzer, and Stoessl 2004; Scott et al. 2008).

The placebo effect might be a learned or conditioned response to the treatment, its environment or ritual, following previous experience of symptom improvement when receiving treatments in certain contexts (Benedetti et al. 2016; Frisaldi et al. 2017). It has been known for a long time that even animals receiving a drug which is later replaced by a placebo continue displaying the effect of the original drug (Herrnstein 1962). Although not using the terms placebo or nocebo, Pavlov and his collaborators showed that dogs who had repeatedly experienced nausea, salivation, vomiting and finally sleep, in response to repeated morphine injections, developed these symptoms in response to the injection of an inert substance, or already in response to the preparation of the injection and in some cases, even in response to the arrival of the experimenter. The more they had been exposed, the more easily the response was elicited (Pavlov, Ivan 1927). Indeed, mechanistically, the placebo effect might in part be similar to Pavlov´s salivating dog.

On a more theoretical level, in a Bayesian framework of brain functioning, our perception is influenced by both the sensory input and the so called prior; the prior probability or belief about the nature of the sensory input. Both shape our ultimate perception and either of them can be given more weight. If the prior, in this case the belief about symptom improvement, is very strong, it will have a strong influence on the final perception.

Whatever the downstream mechanism, the key citing event in a placebo response is the previous experience of or conscious belief in the efficacy of the treatment.

As discussed in (1.2.1 and 1.2.3) the pathophysiology of functional neurological disorders (FND) also seems to involve the prefrontal cortex (Cojan et al. 2009; De Lange et al. 2007; Marshall et al. 1997) and beliefs and expectations.

Given its pathophysiology, one would predict that placebo treatments would be very powerful in FND and indeed, dramatic placebo responses are not infrequently observed and are even part of most definitions of FND (Batla et al. 2013; Edwards, Bhatia, et al. 2011; Edwards, Fotopoulou, and Pareés 2013; Fahn and Williams 1988; Gupta and Lang 2009).

What is unknown, is why the placebo effect can be so strong in FND. Is it because FND patients are more suggestible, because their beliefs play a stronger role in their symptomatology? Or is it because their symptoms are more changeable so that a placebo effect can have a much larger effect than in patients with irreversible damage or degeneration?

1.3 Ethics approval, consent & recruitment

The study was approved by the local ethics committee (London - Bromley Research Ethics Committee, REC reference: 16/LO/1463, IRAS project ID 208265). A major amendment in order to incorporate the placebo study and survey was obtained subsequently. Participants gave their informed written consent to take part in the study. The participant information sheet and consent form following the major amendment are available in appendix A 1. The parts that were irrelevant for each specific subject, were crossed out. Note that an initially planned functional MRI study was not performed.

The healthy control participants were acquaintances of myself or of patients, or recruited from a register of healthy volunteers at University College London.

Patients were recruited from the National Hospital for Neurology, Queen Square, London and St George's Hospital, London. All patients had been diagnosed by a neurologist prior to their inclusion into the study, the vast majority, having been diagnosed by one of the world leading experts in functional neurological disorders / movement disorders, Prof Mark Edwards or Prof Kailash Bhatia respectively. All organic control patients were patients of Prof Bhatia and had therefore been diagnosed by himself prior to inclusion into the study. Three patients with FND found the study via ClinicaTtrials.gov (ID: NCT02905877) and had therefore been diagnosed by a different neurologist.

At the beginning of the study, I double checked each participant's diagnosis by means of a short history and clinical examination. In addition, I made sure there was no functional overlay or cognitive impairment in the case of organic movement disorder patients. With regards to the healthy control participants, I ensured there was no undiagnosed movement or cognitive disorder. The diagnosis of all patients was therefore confirmed by two neurologists.

The exclusion criteria for all participants were:

- Age under 18 or over 80
- Unable to give informed consent for the study procedures due to significant cognitive impairment and/or inability to understand the participant information
- Very severe tremor (except for the placebo study)
- Cognitive impairment

1.4 Programming

All the experiments were performed in a semi-automated way after having been programmed with the programming tool Matlab® R2015b in conjunction with the Cogent 2000 toolbox. Cogent Graphics was developed by John Romaya at the LON at the Wellcome Department of Imaging Neuroscience. The scripts used for the analysis were also programmed with Matlab® R2015b or STATA® (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). All the scripts for the experiments in Matlab and for the analyses in STATA were programmed exclusively by myself. The linear mixed effects model in annexe (A 9.1) was written by Dr Quentin Huys.

Chapter 2 Attention

Overall, the most characteristic feature of functional movement disorders is that they manifest with attention to the affected body part and improve or even disappear completely with distraction. This effect of attention is diagnostic, yet counterintuitive as one might expect attention to the movement to improve performance. Trying to understand if attention is normal and which attentional focus leads to worsening is one of the main aims of this work.

2.1 Attention Network Test

Given the crucial role of attention in functional neurological disorders, an important question is whether attention is normal in this patient group.

The attention network test (ANT), is an elegant task designed by Posner's group that allows to test the alerting, orienting and executive networks' efficiency in a single task (Fan et al. 2002).

Other than through the influence of medications or fatigue, the *alerting* effect is not expected to be affected. The *orienting* aspect is not expected to be abnormal, but a strong focus on the symptom might lead to an inability to shift the attention away from it, onto something else. *Executive* function is the most "conscious" and non-automatic aspect of attention. Since automatic, implicit movements are preserved, but volitional, conscious movements are not, the executive aspect of attention is the one most likely to be affected in functional movement disorders.

2.1.1 Methods

2.1.1.1 Participants

	Healthy control (n=30)	Organic controls (n=30)	Functional neurological disorder (n=30)
M:F	14:16	15:15	13:17
Age (range)	44.7y (24-79y)	48.0y (21-77y)	47.5y (21-79y)
Movement disorder	• none: 30	• Tremor ▪ upper limb: 22 ▪ head: 8 ▪ voice:5 • Weakness: 1 • Dystonia: ▪ cervical: 13 ▪ segmental: 2 ▪ hands / writer´s cramp: 5 ▪ oromandibular:1 ▪ laryngeal: 4 • Myoclonus: 1 • Epilepsy: 1	• Functional tremor: ▪ upper limb: 24 ▪ lower limb: 6 ▪ head: 2 ▪ palate: 1 • Functional weakness: 6 • Functional dystonia: 6 • Functional gait disorder: 5 • Paroxysmal FMD: 4 • NEAD: 5 • Functional myoclonus: 1 • Functional stiffness: 2 • Foreign accent syndrome: 1
medication taken daily that may affect attention	• Antidepressants: ▪ SSRI: 2 ▪ SSNRI: 1	• Benzodiazepines: 3 • Anticholinergics: 1 • Antidepressants: ▪ SSRI: 3 ▪ SSNRI: 1 • Antiepileptic ▪ pregabalin: 1	• Benzodiazepines: 5 • Antidepressants: ▪ SSRI: 6 ▪ SSNRI: 2 ▪ Tricyclic: 2 ▪ Tetracyclic: 1 • Antiepileptic ▪ pregabalin/gapapentin:8 ▪ carbamazepine: 1 • Opioids ▪ non-morphine: 5 ▪ morphine-like: 3 • Neuroleptics: 2
Anxiety HADS – A sub-score (sd)	5.2 (3.5)	7.0 (3.6)	8.9 (4.6)
Depression HADS – D sub-score (sd)	2.4 (2.5)	3.7 (2.4)	8.0 (3.8)

Table 1: Study participant characteristics
All upper limb tremors in the organic control group were action tremors (dystonic tremor, essential tremor and one Wilson´s disease). Note that 15 FND patients and 27 organic controls had more than one movement disorder type and 11 FND and 3 organic controls took more than one analgesic. NEAD (= non-epileptic attack disorder). "Functional gait disorder" means that the gait disorder comprised a functional gait component not explained by any other listed FND type. SSRI=selective serotonin reuptake inhibitor, SSNRI: selective serotonin and noradrenaline reuptake inhibitor. HADS = hospital anxiety and depression scale

2.1.1.2 ANT

The same methods as described in the original paper by Fan et al were used (Fan et al. 2002).

The task (Figure 4) was to respond as quickly as possible to whether an arrow in the centre was pointing to the left or the right. The response was made by pressing a "left" keyboard key with the left hand or a "right" keyboard key with the right hand. Subjects whose symptoms prevented them from using a hand, or whose symptoms would have introduced a marked difference between the two sides, used two fingers of the contralateral hand (5 FND patients).

The target arrow was surrounded by 4 flankers which were either arrows pointing in the same direction as the target arrow (congruent, e.g. → → → → →), arrows pointing in the opposite direction (incongruent, e.g. → → ← → →) or lines (neutral, e.g. -- -- → -- --). Each condition was presented 1/3 of the time. The arrow and the flankers were presented at the same time and were either slightly above or below the fixation cross in the centre.

The target was preceded by one of four cue conditions:

- No cue
- Centre cue
- Double cue
- Spatial cue (either above or below)

The centre, double and spatial cues were temporally informative, as the target arrow always appeared 400ms after the cue. The spatial cue predicted where the arrows were going to be presented (either above or below the fixation cross) with 100% accuracy. Each cue condition was presented ¼ of the time and for 100ms. The fixation cross was shown throughout, and subjects were asked to keep looking at it and not to make any eye movements.

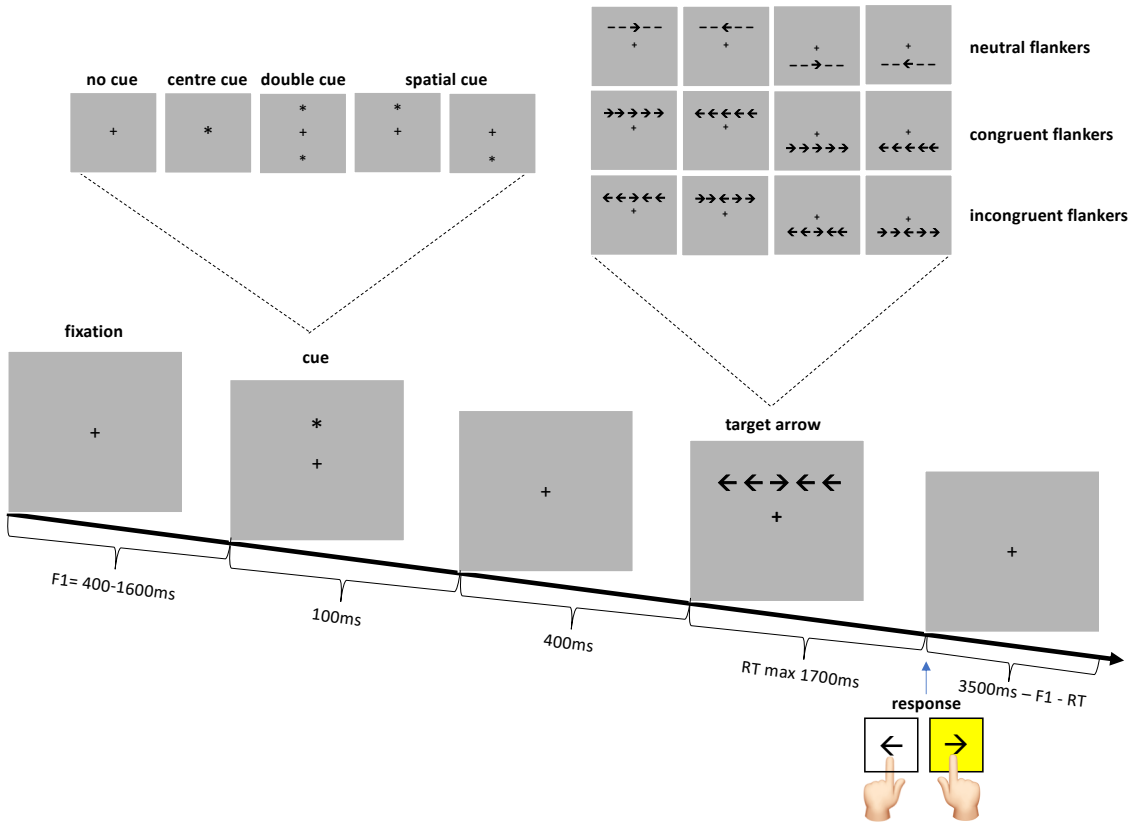


Figure 4: Attention network test experimental setup

The time window given for the response (i.e. the reaction time) was limited to 1700ms. In order to make the appearance of the target less predictable, the display duration of the fixation cross before the cue varied randomly between 400 to 1600ms (in steps of 100). The display of the fixation cross after the response was 1600ms minus the display duration of the fixation cross before the cue, minus the reaction time.

Participants initially performed 24 practice trials in which they were given feedback as to the correctness of the response and their speed (told if too slow).
A total of 288 trials were subdivided into three blocks of 96 trials each with a break in between each block. Trials for which the response time was too slow were repeated once at the end.

The instructions were copied from the online version of the ANT, available on Dr Fan's website (https://www.sacklerinstitute.org/cornell/assays_and_tools/ant/jin.fan/) and expanded slightly so as to make them clearer (see A 3.1). Note that in the online version there were no lines around the central arrow in the neutral condition, whereas in their original paper there were. See A 3.2 for specifications of the sizes of the different stimuli.

2.1.1.3 Exclusions

Trials for which the RT was too slow (>1700ms), even after having been repeated once and incorrect trials were excluded from all analyses. See 2.1.2.2 for error rates. Furthermore, reaction times that fell more than 1.5 times the interquartile range above the 3rd quartile or below the 1st quartile within each subject were excluded as outliers. In the healthy control group 2.8% of trials were excluded as outliers, in the organic tremor groups 2.4% and in the FND group 3.6%.

2.1.2 Results

The age between the three groups was not significantly different (one-way ANOVA $F(2,87)=0.41$, $p=.67$), nor was the male to female ratio (Pearson´s chi-square $\chi^2(2)=0.27$, $p = .87$).

2.1.2.1 Anxiety & depression

The hospital anxiety and depression scale (HADS), is a common screening tool used in clinical practice. It is available in annexe A 2.2. Scores up to 7 are generally considered to be normal, scores of 8–10 indicate mild, 11-14 moderate and 15-21 severe affection.

One-way ANOVA, performed in view of equal variances and equal sample sizes, despite non-normal distributions in the depression sub-score data indicated that there was a significant difference between the three groups both for the anxiety ($F(2,87)=6.87$, $p = .0017$) and the depression sub-score ($F(2,87)=29.7$, $p < .0001$). Post-hoc Šidák corrected two-sample t-tests for the anxiety sub-scores gave a significant difference between the FND group and the healthy controls ($p = .001$), but not for the other group comparisons (FND versus OC: $p = .17$, HC versus OC: $p = .21$).

Since for the depression score, neither control group had normally distributed data, two-sample Wilcoxon rank sum tests were performed. The Šidák-Holm corrected p-values in view of multiple comparisons, remained significant for all comparisons (FND versus HC $p < .001$, FND versus OC $p < .001$, HC versus OC $p = .018$). Thus, FND patients had significantly higher depression scores than their organic counterparts, who themselves had significantly higher depression scores than healthy controls. This fact was reflected in the higher use of antidepressants in the respective groups.

In summary, FND patients had significantly higher anxiety scores on the HADS than healthy controls, but not than their organic counterparts. The depression scores were highest in the FND group, followed by the organic group and lowest in the healthy controls. The higher antidepressant use in the patient groups reflected these differences. These findings were taken into account in the analysis (see 2.1.2.4 and A 3.3 for details).

2.1.2.2 Error rate

The error rate (pressed the wrong key in response to the central arrow) for congruent, neutral and incongruent flankers for each group is summarised in Table 3 and visualised in Figure 5. As expected, most errors occurred with incongruent flankers and indeed the error rates were similar to those found in Fan´s original paper.

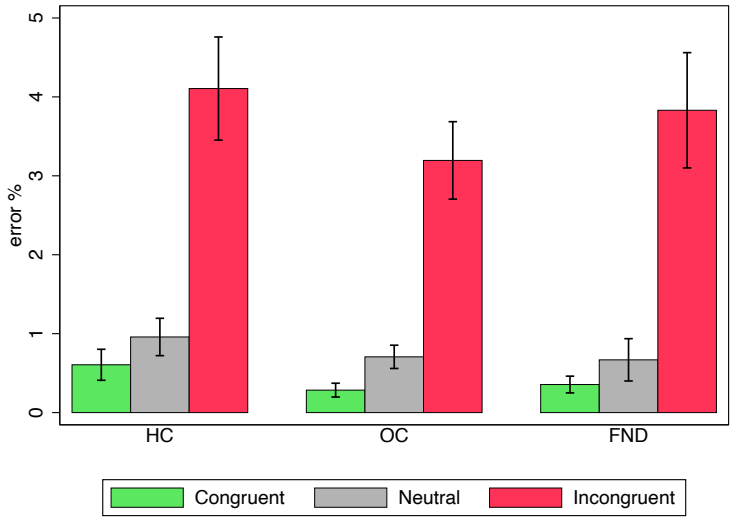


Figure 5: Errors according to flanker type
The error bars indicate the standard error of the mean

	Shapiro-Wilk normality test (*p*-value)		
	Congruent flankers	**Neutral flankers**	**Incongruent flankers**
HC (n=30)	**<0.0001**	**0.00025**	**0.0025**
OC (n=30)	**<0.0001**	**0.00023**	**0.018**
FND (n=30)	**<0.0001**	**<0.0001**	**<0.0001**
Levene	**0.0.0030**	0.25	0.32

Table 2: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

	Congruent flankers (sd)	**Neutral flankers** (sd)	**Incongruent flankers** (sd)
HC (n=30)	0.61% (1.08)	0.96% (1.30)	4.1% (3.6)
OC (n=30)	0.28% (0.48)	0.71% (0.81)	3.2% (2.7)
FND (n=30)	0.36% (0.58)	0.67% (1.47)	3.8% (4.0)
Kruskal-Wallis	$\chi^2(2)$ with ties =0.99	$\chi^2(2)$ with ties =1.97	$\chi^2(2)$ with ties =0.81
	p = .61	p = .37	p = .67

Table 3: Error according to flanker type

As can be seen in Table 2 the assumptions underlying the mixed model ANOVA were not met (unequal variances between the groups in the congruent flanker condition, and not one of the group and flanker type data points were normally distributed). A Kruskal-Wallis test for each flanker type separately was therefore performed (Table 3). Since none of these showed a significant difference between the three groups, in order to determine whether the error rates differed between the three flanker types, the flanker types irrespective of group were compared to each other by means of a Kruskal-Wallis test (in view of non-normal distributions of each flanker type and inequality of variance between the three (Shapiro-Wilk $p < .0001$ for all three and Levene: 0<0.0001)). The Kruskal-Wallis test showed a significant difference between the three flanker types ($\chi^2(2)$ with ties =107.7, $p = .0001$) and Holm-Šidák corrected two-sample Wilcoxon rank-sum tests were highly significant between the incongruent and either of the other flanker types ($p < .0001$).

In summary, there were no significant differences in the error rates between the three groups and all three groups made significantly more errors in response to the incongruent flankers.

2.1.2.3 Overall reaction time

	RT in ms (*sd*)
HC (n=30)	605 (95)
OC (n=30)	639 (97)
FND (n=30)	725 (144)
One-way ANOVA	$F(2,87)=8.74$, $\eta 2 = .17$
	***p* = .0003**

Table 4: Group average reaction times for all conditions

Since each group´s reaction time had a normal distribution (Shapiro-Wilk for HC $p = .32$, OT $p = .38$, FND $p = .16$), and the variances between groups were not unequal (Levene´s test for equality of variance $p = .068$), a one-way ANOVA was performed, which was significant (Table 4). Post-hoc two-sample t-tests with Šidák correction show that the FND was significantly slower than either control group (FND versus HC $p < .0001$, FND versus OT $p = .015$) and that there was no significant difference between the two control groups ($p = .57$).

In summary, FND patients had significantly slower overall reaction times than the control groups.

2.1.2.4 Alerting, orienting and conflict effect

As in the original paper, the alerting, orienting and conflict effects were calculated in the following manner for each subject:

Alerting effect = RT No cue – RT double cue

Orienting effect = RT centre cue – RT spatial cue

Conflict effect = RT incongruent − RT congruent

Note that for the alerting effect the double cue was used as it is postulated that in both the "no cue" and the "double cue" the attentional focus is large. Hence the only difference is the timing information. For the orienting effect, on the other hand, the control was the single central cue as it leads to attention to one location, similar to the spatial cue. The spatial cue is both spatially and temporally informative, the alerting cue on the other hand is only temporally informative, thus the difference in reaction time between the two gives the orienting effect.

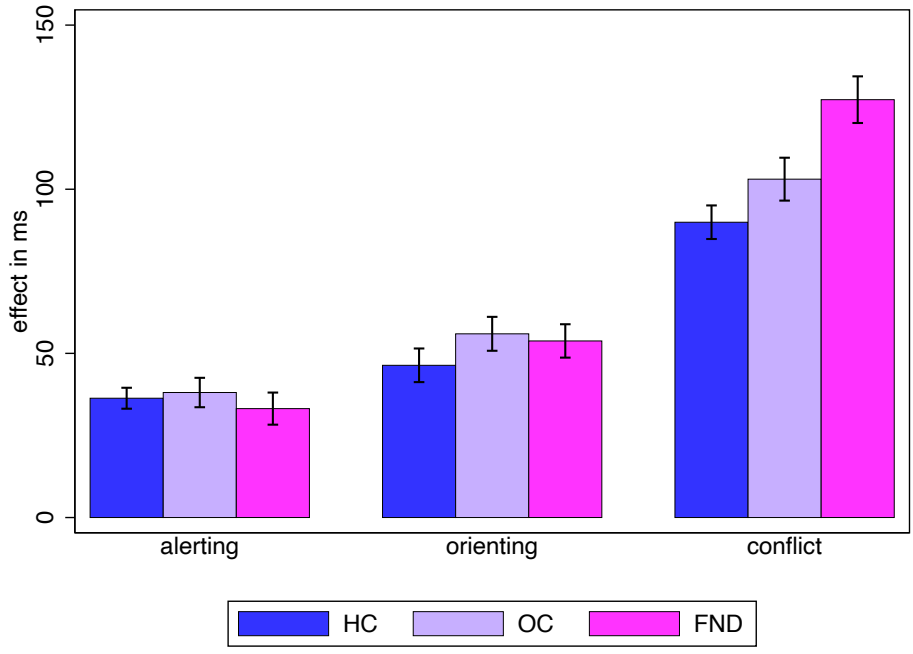


Figure 6: Alerting, orienting & conflict effect group averages
The standard error of the mean is shown by the error bars.

The interesting question is whether there is a difference in the effects between the three groups in each condition. The question is not if the size of the alerting, orienting and conflict effect differ.

A simple one-way ANOVA was therefore performed for each condition. Checking the underlying assumptions (Table 5), the FND group's orienting effects and the organic movement disorder

group's conflict effects were not normally distributed, but since the sample sizes were equal and there was homogeneity of variance, one-way ANOVA could be used for each effect.

	Shapiro-Wilk normality test (*p*-value)		
	Alerting	**Orienting**	**Conflict**
HC (n=30)	0.77	0.51	0.17
OC (n=30)	0.60	0.82	**0.0056**
FND (n=30)	0.11	**0.0081**	0.76
Levene	0.12	0.84	0.12

Table 5: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

	Alerting (*sd*)	**Orienting** (*sd*)	**Conflict** (*sd*)
HC (n=30)	36.3 (17.4)	46.4 (28.0)	90.0 (28)
OC (n=30)	38.1 (24.5)	56.0 (28.3)	103.1 (35.8)
FND (n=30)	33.2 (26.8)	53.8 (27.9)	127.3 (38.9)
One-way ANOVA	$F(2,87)=0.34$ $\eta^2 = .008$	$F(2,87)=0.96$ $\eta^2 = .022$	$F(2,87)=9.03$ $\eta^2 = .17$
	$p = .71$	$p = .39$	$\boldsymbol{p = .0003}$

Table 6: Alerting, orienting & conflict effect group averages (in ms)

One-way ANOVA was significant in the conflict effect. Šidák-Holm corrected pairwise comparisons confirmed that there was a significant difference between the FND group and either control group (FND versus HC two-sample t-tests $t_{uncorr}(58)=-4.27$, $p_{corr} < .0002$, FND versus OT Wilcoxon rank sum test: $z_{uncorr} = -2.53$, $p_{corr} = .023$), but not between the two controls (Wilcoxon rank sum test: $z_{uncorr} = -1.21$, $p_{corr} = .23$).

In the original paper by Fan et al, the alerting effect was 47ms, the orienting effect 51ms and the conflict effect 84ms, similar to this study´s healthy controls.

So as to exclude that the observed difference between the groups was caused by medications or additional medical conditions that can affect attention, the analysis was repeated after all subjects on relevant medication (benzodiazepines, opioids, antiepileptics, antidepressants, anticholinergics) were excluded. Note that this also excluded subjects with chronic pain, depression or anxiety important enough to warrant medication. The conclusions for the alerting, orienting and conflict effect remain nevertheless the same. Details are available in A 3.3.

Fatigue, which is a common symptom in FND, could have an effect on attention, but this would be expected to also affect the alerting component, and not selectively the executive system.

In order to double check that it was really the incongruent flankers inhibiting patients with FND more, rather than congruent ones facilitating them more, Figure 7 displays the groups´ reaction times for the congruent, neutral and incongruent flankers.

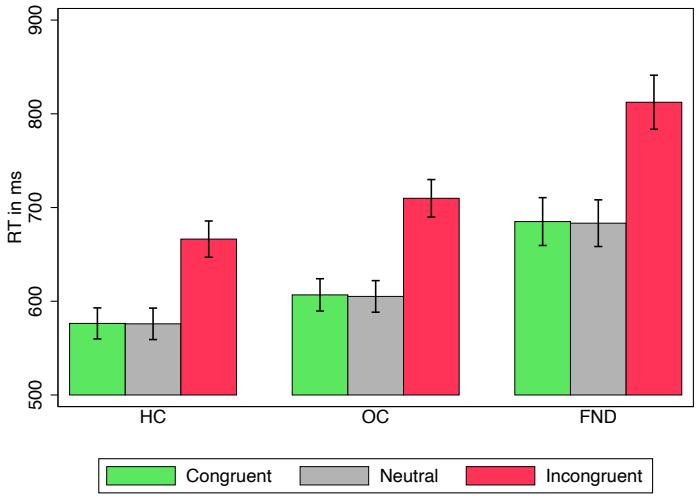


Figure 7: RT with congruent, neutral and incongruent flankers

It is clear that the reaction times with congruent flankers were unchanged from those with neutral flankers and that it was the incongruent flankers that lead to slower reaction times, particularly in the FND group.

Note that responses with the more affected side (which could include an ipsilateral body part other than the arm) in subjects with asymmetric symptoms (FND 15 patients, OT 25 patients), were not significantly slower in either group compared to the responses with the less affected side (one-sample t-test of the difference between the more and less affected side in FND: $p = .62$, in OT $p = .35$. Both were normally distributed).

The fact that patients with FND had overall slower reaction times cancelled itself out, given there were equal numbers of left and right responses and the alerting, orienting and conflict effects are calculated by subtracting the reaction time with one type of cue or flanker from another.

In summary, patients with FND had normal orienting and alerting network efficiencies but showed a deficit in the executive network compared to healthy and organic patients. This effect was independent of medication use and was due to larger difficulties with incongruent flankers.

2.1.3 Interim discussion

In summary, the alerting and orienting network's efficiency is normal, but the executive network is abnormal in functional neurological disorder patients compared to healthy controls and organic neurological controls. In particular, it is the conflict or incongruence that hinders FND patients more than controls.

This contradicts the common notion of preserved attention in FND but is in line with the clinical picture. Patients with FND often complain of inability to multitask; even simple tasks seem very effortful and indeed part of their fatigue might be secondary to their difficulties due to executive dysfunction.

Previous studies were particularly interested in motor planning. They showed that when endogenous stimuli allowed the planning of the subsequent motor response (knowing which motor response was going to be required), healthy controls responded faster, but functional movement disorder patients did not. With exogenous stimuli, which automatically attract attention, reaction times were normal. The interpretation was that conscious motor control is abnormal in FMD. (Pareés et al. 2013; Roelofs et al. 2003; Teodoro, Meppelink, et al. 2018)

The current study is different, since the cue does not give any indication on which motor response will be required – it only indicates when or where the target arrow will appear, but not whether it will be pointing to the left or the right. Thus, the current study concerned visual attention and attentional resources in general, not motor preparation.

A previous ANT study on patients with chronic fatigue syndrome with depression, without depression and a healthy control group, showed no significant difference between the two patient groups. Alerting and orienting effects were normal in both patient groups. For the conflict effect it showed a trend towards increased durations in both patient groups compared to healthy controls. This did, however, not reach statistical significance. (Togo et al. 2015)

A modified version of the ANT, the ANT-I, was performed in fibromyalgia patients. In this modified version, the alerting cue is a tone presented before the visual cue, the cue validity is only 50% i.e. non-informative and there are only two flanker types, namely congruent and incongruent flankers. Performing this modified ANT, fibromyalgia patients showed an impairment of both the alerting and the executive components of attention. (Miro et al. 2015) Pain is the main feature of fibromyalgia and a well-known influencer of attention.

As with every finding, the big question is whether this abnormal executive function is a cause or an effect of the FND. Executive dysfunction could be partly secondary to the attentional resources being taken up by the functional symptoms, and hence not being available for other tasks.

2.2 "Natural" attentional focus in functional tremor

An important question is where the subjects´ attentional focus naturally lies and if it differs between functional neurological disorder patients and healthy and organic control subjects.

- Is attention focused on the target?
- Is attention focused on the movement?
    - If so which aspect of the movement is it focused on?
        - Visual feedback
        - Proprioceptive motor information
- Is attention focused neither on the target nor the movement, but elsewhere?

2.2.1 Methods

2.2.1.1 Participants

Although attention is likely to play a role in most functional neurological disorders, it was decided to test patients with a tremor. The advantage of movement disorders is that they are not subjective sensations which are inherently difficult to quantify, but instead can be measured objectively. Within functional movement disorders, the easiest group to study are patients with tremor. Tremor can easily and rapidly be modulated, it is easily measured, and even healthy subjects sometimes present a tremor, typically under stress or fear. Thus the subjects for all the reaching experiments (0 and 2.3) were patients with a functional action tremor and two control groups: patients with an organic action tremor (essential, tremor, dystonic tremor and one case of Wilson´s disease) and healthy controls. Both control groups were age and gender matched.

Including two groups of controls; healthy individuals and patients with the organic counterpart, was essential in order to be able to differentiate the functional aspects from those related to the presence of a tremor. Many studies in the past have only compared functional movement disorders to healthy controls. Any difference found was attributed to the functional disorder. However, this difference might as well have been due to the presence of the movement disorder, and not due to its functional nature.

Table 7 summarises the characteristics of the participants for the deviation and target jump conditions, Table 8 for the luminance conditions. See appendix A 4.1 for details.

	Action tremor type	Age average (range)	M:F	Visual acuity average (*sd*)
HC (n=24)	0	42.9 (21-68)	10:14	95.8 (8.8)
OT (n=21)	• Dystonic tremor: 16 • Essential tremor: 4 • Wilson´s disease: 1	53.6 (21-78)	11:10	99.5 (2.2)
FND (n=25)	• Functional tremor: 25	51.8 (21-75)	11:14	87.8 (17.4)

Table 7: Participants' characteristics for the deviation and target jump conditions

For the deviation and target jump conditions age was not significantly different between the three groups. Binocular corrected visual acuity was significantly worse in the FND group compared to the OT group but not compared to the HC group.

	Action tremor type	Age average (range)	M:F	Visual acuity (*sd*)
HC (n=27)	0	43.6 (21-79)	12:15	95.6 (13.9)
OT (n=22)	• Dystonic tremor: 19 • Essential tremor: 2 • Wilson´s disease: 1	52.0 (21-78)	14: 8	98.0 (5.5)
FND (n=28)	• Functional tremor: 28	51.6 (21-74)	13:15	90.0 (14.4)

Table 8: Participants' characteristics for the luminance conditions

For the luminance conditions, neither age nor visual acuity were significantly different between the three groups.

Only one subject, who had been known for a longstanding dystonic tremor, but on the day of the experiment showed clear signs of distractibility and hence functional overlay was excluded.

2.2.1.2 Reaching movement

All the conditions involved a simple reaching movement of the index finger on a touchpad from a starting position to a visual target straight ahead. The hand and arm were hidden underneath a horizontal screen onto which the target and current hand positions were projected (Figure 8). This setup removed the direct visual feedback from the hand, and additionally allowed dissociation of visual feedback from proprioceptive-motor information (see below).

Figure 8: Box on setup
In the box on condition, the subject´s hand and the touchpad on which the finger was moved were hidden underneath a horizontal screen (20-inch with a refresh rate of 60Hz) onto which the start, target and the current finger positions were projected in real time.

The participants were told to slide their finger from the starting position to the target in one straight movement, without lifting their finger off the touchpad and at a comfortable speed. (Figure 9)

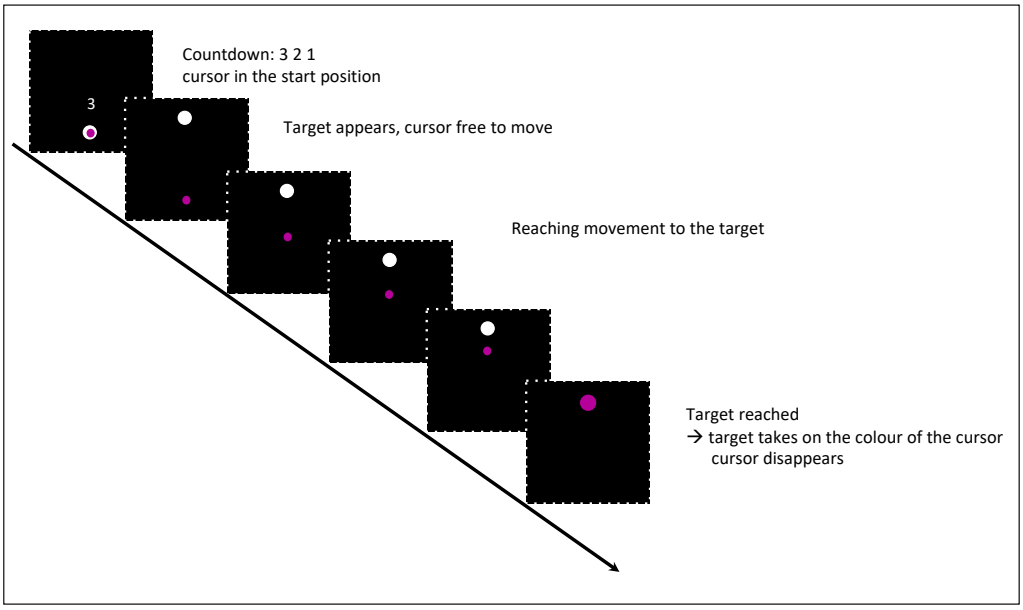


Figure 9: Reaching movement

A classic way of testing attention is via the measurement of detection thresholds. Thus, the detection thresholds involving different aspect of the reaching movement were determined for the three groups.

- Proprioceptive motor aspect – added deviation
- Target – target jump and target luminance change
- Visual feedback – cursor luminance change

2.2.1.3 Added deviation

Hiding the hand and arm underneath a horizontal screen onto which the target and current hand positions were projected removed the direct visual feedback from the hand, thereby allowing dissociation of visual and proprioceptive-motor aspects of attention to movement. Unknown to the participant, an angular deviation was added to the visual feedback of their hand position. In other words, even though they moved their finger straight ahead, the corresponding finger cursor they saw deviated to either side, by a fixed angle (Figure 10). Previous studies have shown that healthy subjects automatically adjust their trajectory so as to make the resulting visual feedback move in a straight line. They only detect such an added deviation once it rises above approximately 14º. (Slachevsky et al. 2001)

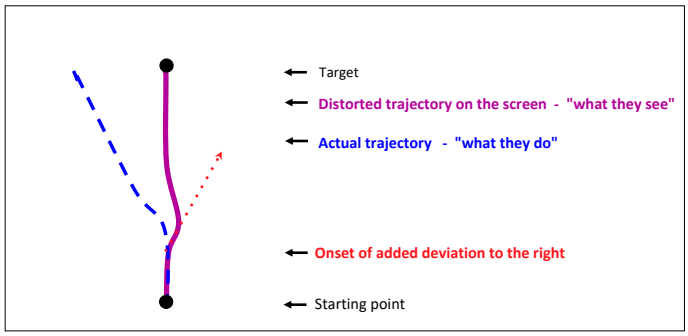


Figure 10: added angular deviation
Added angular deviation to the visual feedback and subject's automatic correction. Adapted from (Fourneret and Jeannerod 1998)

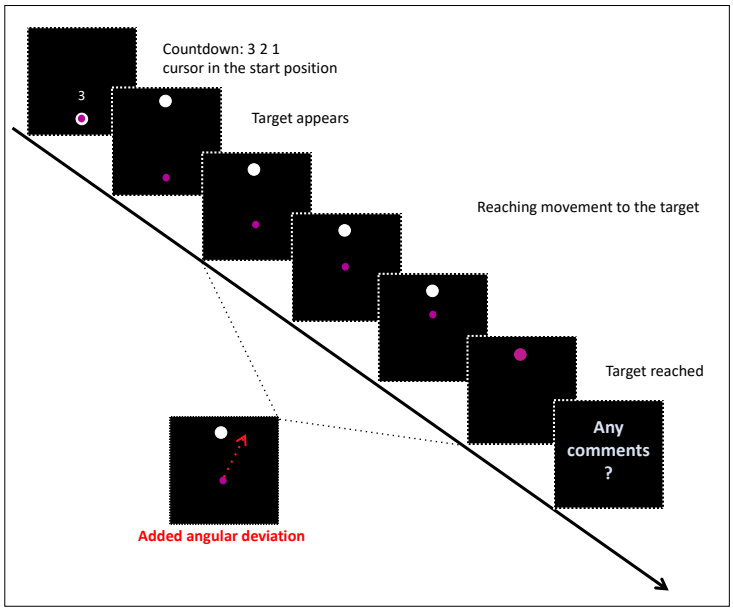


Figure 11: Added deviation threshold condition
After a certain number of baseline trials, the visual feedback was distorted by an added deviation which increased by 1º from trial to trial and randomly varied to the left or right. In each specific trial, the amplitude of the added angular deviation remained constant and persisted to the end of the trial. After each trial the subjects were asked to press a yes or no button in response to the question if they had any comments to make. Their spontaneous detection threshold was thereby determined.

If patients with FND attend more to visual feedback than controls, a higher threshold is predicted - proprioceptive feedback needs to be highly discrepant to signal that their action differs from what they see. Their tendency to gaze at their affected limb predicts this result (Van Poppelen et al. 2011). If, conversely, they attend more to internal, proprioceptive information, then their threshold for detecting deviation will be below normal.

2.2.1.4 Target jump

If the subjects' attentional focus naturally lies on the target (the target dot they need to reach), then one can expect them to have a low threshold for detecting that the target randomly jumps to the left or right during their reaching movement. This task is commonly known as the double step experiment and here it will be called the "Target jump condition" (Figure 12).

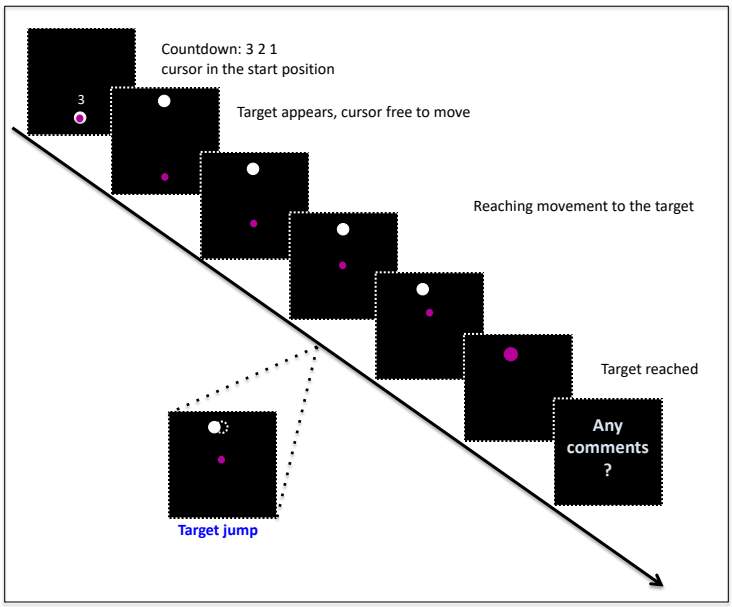


Figure 12: Target jump threshold condition
After a certain number of baseline trials, the target jumped randomly to the left or right once during the reaching movement and the amplitude of this target jump increased from trial to trial. After each trial the subject was asked to press a yes or no button in response to the question if they had any comments to make. Subjects were not told in advance that the target would jump, they needed to detect it spontaneously.

2.2.1.5 Spontaneous, absolute & 75% correct detection thresholds

For the target jump, the added deviation and the target and the cursor luminance change threshold conditions (see below) the spontaneous detection threshold was determined first. When subjects spontaneously detected the respective change, they were asked how many times they had noticed it before without saying anything – this was the spontaneous detection threshold.

The condition was then repeated twice, with the subject knowing which change to look out for. The best detection threshold of the two was retained as the absolute detection threshold.

The amplitude yielding a 75% correct response was then determined and used for all subsequent conditions in which this respective change had to be detected.

The order of the conditions was randomised.

2.2.1.6 Luminance changes

For all the conditions in which the luminance of either the target or the cursor changed during the reaching movement, both the cursor and the target were of equal size (15 pixels) and their initial colour was white ([1,1,1] in RGB (using a range of 0-1 for the intensity of the Red, Green and Blue component)). This was necessary so as to make both changes equally salient.

The participants were not informed in advance that the cursor had been increased to the size of the target and the trial number at which they detected it was noted.

The luminance change persisted for the duration it took the participant to move along by 25% of the direct trajectory and then reverted back to white. The first luminance change occurred at the earliest after 25% of the direct trajectory and the last luminance change back to the original white colour occurred at the latest after 75% of the direct trajectory. The change occurred randomly when the cursor reached one of five different locations along the trajectory. Thus, the change occurred at 25-50%, 31.25-56.25%, 37.5-62.5%, 43.75-68.75% or 50-75% of the trajectory. The luminance change became more and more marked from trial to trial, until it was detected by the participant. The original colour of the target, or the cursor respectively, was white ([1,1,1] in an RGB scale, using a range of 0-1 for the intensity of the Red, Green and Blue component). The color changed by [0.05,0.05,0.05] from trial to trial ([0.95, 0.95, 0.95], then [0.9, 0.9, 0.9] etc.), i.e. it changed from white to a gradually darker grey (see Figure 13).

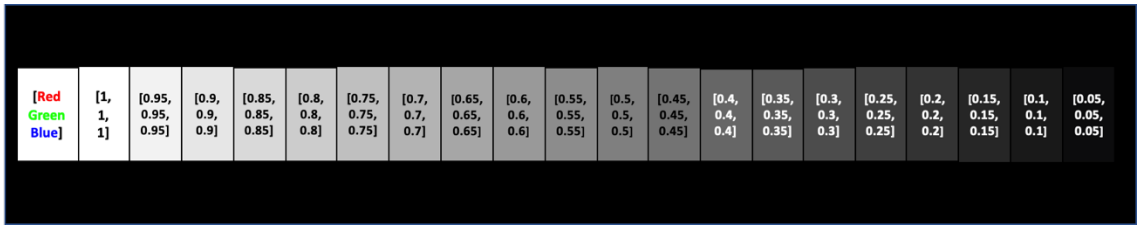


Figure 13: Luminance changes
The resulting grey tones/ luminance changes are shown, together with the RGB code (using a range of 0-1 for the intensity of the Red, Green and Blue component)

2.2.1.6.1 Target luminance change

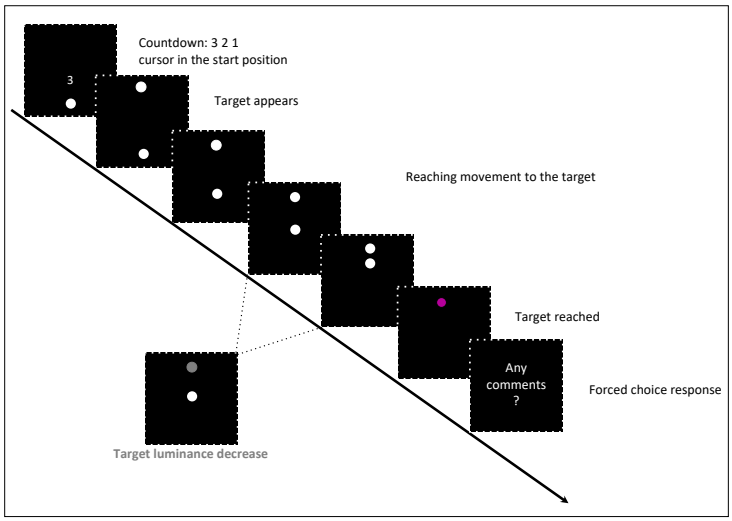


Figure 14: Target luminance threshold condition

During the reaching movement, the target changed luminance for the time it took the participant to move along 25% of the direct trajectory. Following this, it reverted back to its original white colour.

2.2.1.6.2 Cursor luminance change

The setup was identical to the target luminance change, with the only exception that it was not the target, but instead the cursor that changed luminance during the reaching movement.

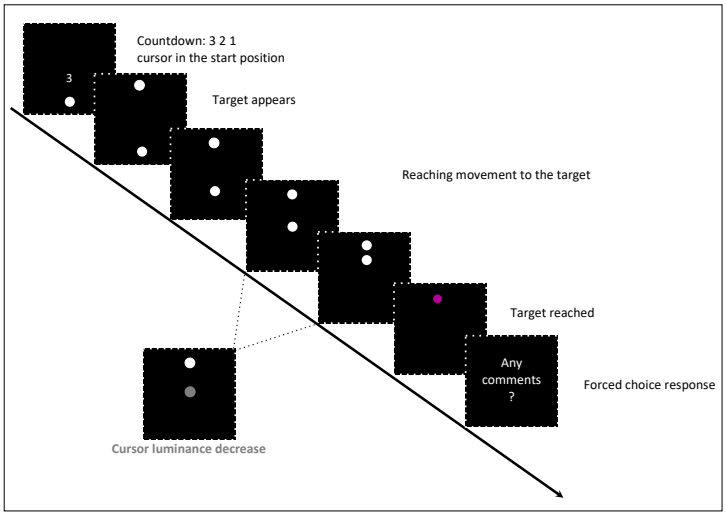


Figure 15: Cursor luminance threshold condition

2.2.1.6.3 Target versus cursor luminance change

The spontaneous detection threshold contains some recall bias and some estimation by the subjects as to how many times they had perceived the change without making any comment. The absolute and the 75% detection thresholds, partly measure a subject´s natural attentional focus, but they are also partly a measure of how well the subjects are able to shift their attention to the required aspect of their movement.

A more rigorous way of detecting where the attentional focus naturally lies is to use a signal detection approach, directly comparing attention to the target and the visual feedback of the movement, i.e. the cursor.

In this condition, subjects were told that in any of the trials, either the cursor, the target, both the cursor and the target or neither of them were going to transiently change in brightness as they moved the cursor towards the target. Their task was to reply after each trial whether or not the cursor had changed in brightness and whether or not the target had changed in brightness (Figure 16).

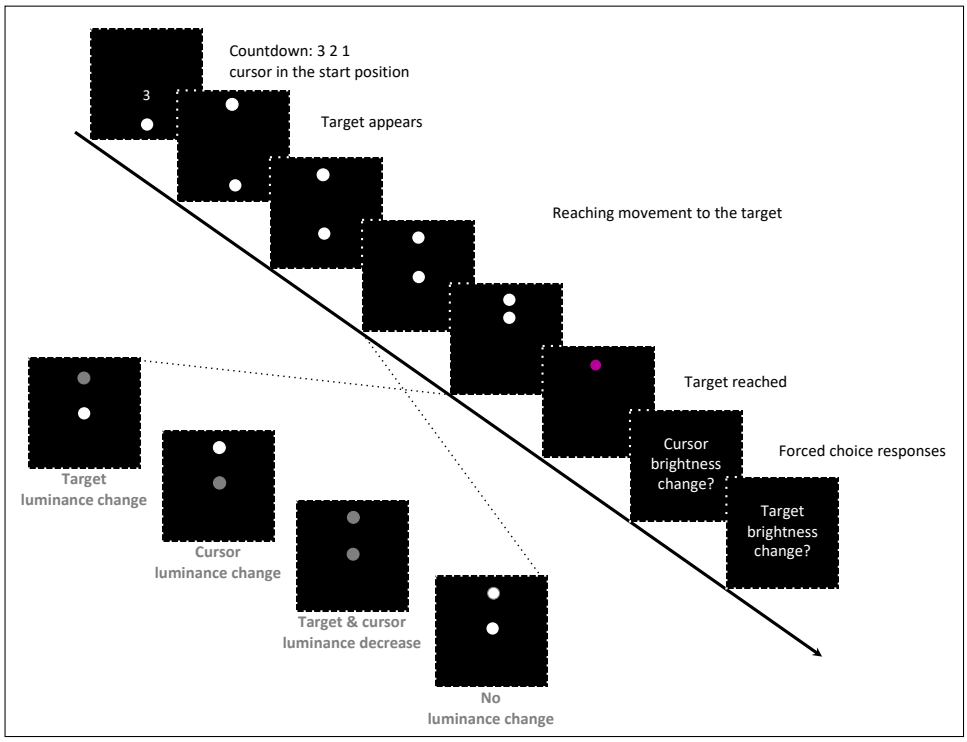


Figure 16: Cursor versus target luminance change

It was important that subjects performed the movement in their usual manner. They were told that they were not supposed to detect 100% of the changes and that they should not move slowly and keep looking back and forth between the cursor and the target. Instead, they were told to perform the movement at their usual speed, the way they would do it if there was nothing to look out for and simply report the luminance changes they noticed. See A 4.2 for the written instructions, which were complemented verbally.

The luminance change amplitudes were adapted to each participant. The smallest change corresponded to their worst absolute detection threshold for either the target or the cursor and the other changes were 0.1, 0.2 and 0.3 in RGB scales more marked (Figure 13). These individualised luminance changes ensured that the difficulty of the task was adapted to each subject, thus avoiding ceiling effects with 0% or 100% hit rates. Additionally, the use of four different intensities increased the variability in the responses, again avoiding ceiling effects.

In ¼ of the total number of trials the cursor changed luminance, in ¼ the target, in ¼ both and in ¼ neither of them changed luminance. With a total of 60 trials this led to 30 trials in which the cursor changed luminance (cursor changed + cursor and target changed) and 30 in which it did not (target changed + neither changed). With the equivalent numbers for the target change.

2.2.2 Predictions

According to the hypothesis that functional tremor patients pay little attention to the target but instead to their movement, and in particular its visual feedback rather than proprioceptive-motor information, they were expected to be worse than either control group at detecting the target jump, the target luminance change and the added deviation, but better at detecting the cursor luminance change. In the cursor versus target luminance change in particular, functional tremor patients were expected to detect more changes of the cursor, in contrast to the controls who were expected to detect more target changes.

2.2.3 Results

2.2.3.1 Added deviation detection threshold

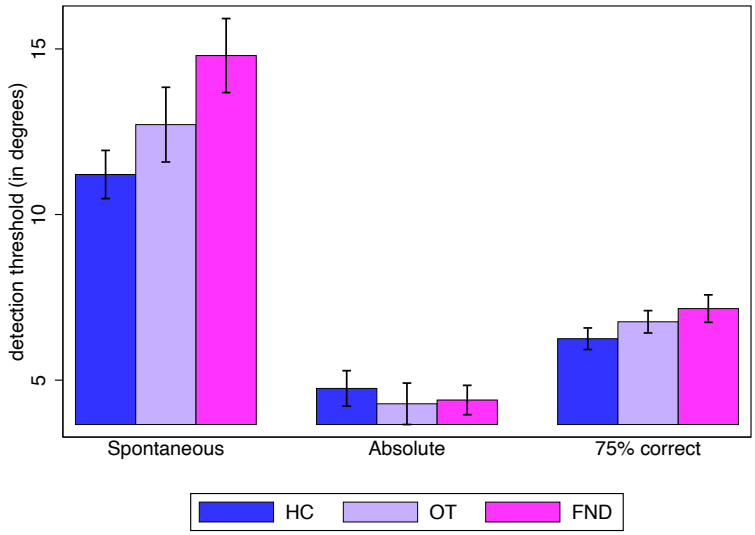


Figure 17: Added deviation detection thresholds
The group averages for the spontaneous and the absolute detection thresholds, in addition to the threshold leading to 75% correct detection are shown. The error bars indicate the standard error of the mean.

Assumptions check

	Shapiro-Wilk normality test (*p*-values)		
	Spontaneous detection threshold	**Absolute detection threshold**	**75% correct detection threshold (actual percent correct responses)**
HC (n=24)	0.46	0.32	0.74 (72.4% correct)
OT (n=21)	0.59	0.065	0.10 (74.0% correct)
FND (n=25)	0.25	0.88	**0.0010** (76.0% correct)
Levene	***p* = .041**	*p* = .56	*p* = .69

Table 9: Shapiro-Wilk normality test, Levene's test of homogeneity of variance, percent correct responses
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

Practice trials identified the angle of added deviation that lead to an approximately 75% correct detection. When evaluating the actual hit percentage (i.e. correct detection) in the deviation / no deviation condition (see 2.3.4.1), the actual percentage of correct detection was not significantly

different from 75% for either group (one-sample t-test with a hypothesised mean of 75 HC: p = .55, OT: p = .82 and FND: p = .83), thus the detection thresholds of the three groups can be compared to each other.

	Spontaneous detection threshold (group average in degree) (*sd*)	**Absolute detection threshold** (group average in degree) (*sd*)	**75% correct detection threshold** (group average in degree) (*sd*)
HC (n=24)	11.2 (3.6)	4.8 (2.6)	6.3 (1.6)
OT (n=21)	12.7 (5.2)	4.3 (2.9)	6.8 (1.5)
FND (n=25)	14.8 (5.6)	4.4 (2.2)	7.2 (2.1)
One-way ANOVA		$F(2,67)=0.21$	$F(2,67)=1.63$
		p = .82	p = .20
Kruskal-Wallis	$\chi^2(2)$ with ties=6.77		
	***p* = .034**		

Table 10: Added deviation detection thresholds

For the spontaneous detection threshold, a Kruskal-Wallis test was performed in view of the unequal variances between the groups. It indicated a statistically significant difference between the three groups. Šidák-Holm corrected two-sample t-tests in view of the normal distribution of all groups, gave a significant difference between the FND and HC (p = .021), but not between the FND and the OT (p = .20).

One-way ANOVA was not significant for the other detection thresholds (absolute and 75% correct detection thresholds, see Table 10).

In summary, the spontaneous detection of an added deviation is worse in FND patients compared to healthy controls, but not compared to organic controls.

2.2.3.1 Target jump detection threshold

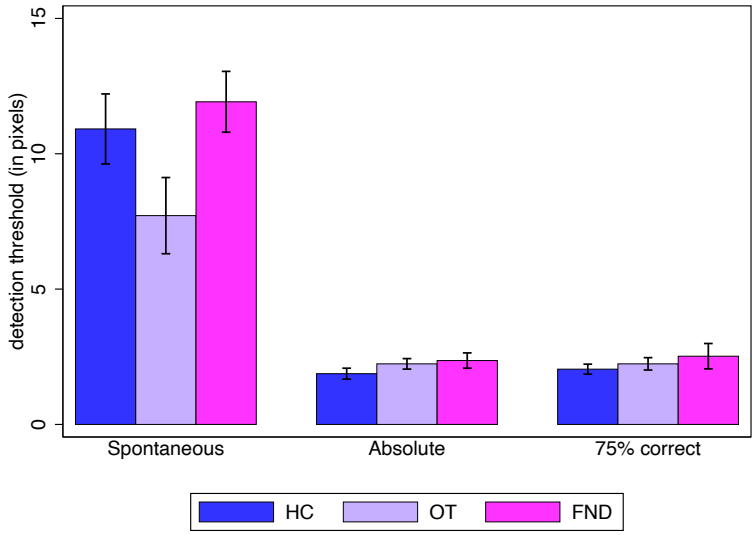


Figure 18: Target jump detection threshold
The group averages for the spontaneous and the absolute detection thresholds, in addition to the threshold leading to 75% correct detection are shown. The error bars indicate the standard error of the mean.

	Shapiro-Wilk normality test (*p*-values)		
	Spontaneous detection threshold	**Absolute detection threshold**	**75% correct detection threshold**
HC	0.97	**0.0014**	**0.0044** (76.8% correct)
OT	**0.0024**	0.84	**0.047** (75.0% correct)
FND	0.70	**0.0019**	**<0.0001** (66.0% correct)
Levene	$p = .76$	$p = .20$	$p = .030$

Table 11: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

Practice trials identified the jump amplitude that lead to an approximately 75% correct detection of the target jump. Additionally, when evaluating the actual hit percentage (i.e. correct detection) in the jump / no jump condition (2.3.6.1.1), the actual percentage of correct detection was not significantly different from 75% for either group (one-sample t-test with a hypothesised mean of 75 HC: $p = .72$, OT: $p = .99$ and FND: $p = .071$), thus the detection thresholds of the three groups can be compared to each other.

	Spontaneous detection threshold (group average in pixels) (*sd*)	**Absolute detection threshold** (group average in pixels) (*sd*)	**75% correct detection threshold** (group average in pixels) (*sd*)
HC (n=21)	10.9 (6.3)	1.9 (1.0)	2.0 (0.91)
OT (n=21)	7.7 (6.5)	2.2 (0.89)	2.2 (1.0)
FND (n=22)	11.9 (5.6)	2.4 (1.4)	2.5 (2.3)
One-way ANOVA	$F(2,67)=2.87$	$F(2,67)=1.2$	
	0.064	$p = .31$	
Kruskal-Wallis		$\chi^2(2)$ with ties=3.15	$\chi^2(2)$ with ties=0.38
		$p = .21$	$p = .83$

Table 12: Target jump detection thresholds

A one-way ANOVA for the spontaneous detection threshold of a target jump showed a trend at $p = .064$. Šidák-Holm corrected two-sample Wilcoxon rank-sum tests revealed that the difference between the FND group and the OT group was significant ($p = .027$), but the difference between the OT and HC was not ($p = .14$). The difference between FND and HC was not significant either (Šidák-Holm corrected two-sample t-test $p = .56$.

The absolute detection threshold, i.e. the actual detection threshold when warned that there might be a target jump was not significantly different between the groups, nor was the "75% correct" detection threshold (see Table 12)

In summary, only the spontaneous detection threshold showed a possible difference between the groups, in that there was a trend for the OT to be better. There was, however, no difference between the FND and HC groups.

2.2.3.2 Spontaneous detection of cursor size change

So as to make the salience of the luminance changes equal, the cursor size was increased to the size of the target (previous cursor size of 10 pixels diameter increased to 15 pixels). The percentage of subjects within each group who noticed it (either mentioned it spontaneously or when asked) is summarised in Table 13.

	Spontaneously detected cursor size change
HC (n=27)	7.4%
OT (n=22)	22.7%
FND (n=28)	35.7%
Fisher's exact test	***p* = .033**

Table 13: Percentage of subjects who spontaneously noticed the cursor size change

Given the expected frequency in one of the cells was <5 (4.9), the assumptions of normality for the Chi-square test were not met and thus Fisher's exact test was applied. This gave a significant effect (p = .033).

Post-hoc analyses showed that the difference between the two tremor groups was not significant (Pearson´s chi-square $\chi^2(1)=0.98$, p = .32), nor was the difference between the two control groups (Fisher´s exact test p = .22), but the difference between the FND and the HC was (Pearson´s chi-square $\chi^2(1)=6.46$, p = .011). After Šidák-Holm correction for multiple comparisons, the difference between the FND and the HC remained significant (p = .033).

In summary, more FND patients than healthy controls, but not than organic controls, noticed that the cursor had changed in size

2.2.3.3 Target and cursor luminance change detection thresholds

Since the two conditions were identical apart from the object that changed its luminance, the two were compared directly by means of a mixed model ANOVA with group as between-subject factor and object (target versus cursor) as within-subject factor. This of course as long as its assumptions were met. Note nevertheless, that given the continuous movement of the cursor, contrasting to the stationary target, it was expected to be slightly more difficult to discern a luminance change in the cursor than in the target.

Spontaneous detection threshold

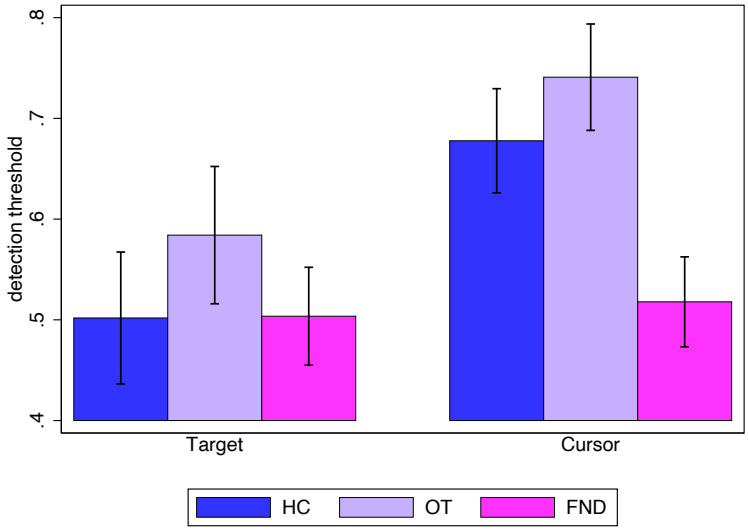


Figure 19: Spontaneous detection threshold for the target and the cursor luminance change
This amplitude change from the original white colour [1 1 1] in ([R G B] = [y y y]) colour code is shown as the detection threshold. The SEM is shown by the error bars.

Note that the detection threshold was measured in terms of the colour change that was necessary for detection. It indicated by how much each of the Red Green and Blue colour in the [R G B] colour scheme had to change on a scale from 0 to 1. Since the colour changed from white [1 1 1] to a grey tone, each one of the Red Green and Blue values was identical. A detection threshold of 0.7 for example, meant the change in luminance was detected when the object changed from its original white [1 1 1] to [0.3 0.3 0.3] (see Figure 20).

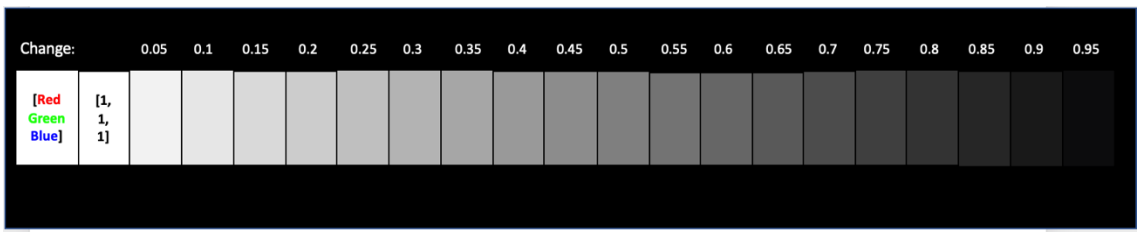


Figure 20: Changes in luminance
The resulting grey tones are shown with the corresponding changes (change of each of the [R G B] from the original white [1 1 1])

	Shapiro-Wilk normality test	
	Target spontaneous detection threshold	**Cursor spontaneous detection threshold**
HC (n=27)	0.59	0.58
OT (n=22)	0.28	0.32
FND (n=28)	0.20	0.36
Levene	p = .094	p = .65

Table 14: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The p-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

Mixed model ANOVA

For the spontaneous detection thresholds, mixed model ANOVA with group as between subject factor and object (target versus cursor) as within subject factor was performed in view of the normal distribution for all six combinations and equality of variance between the groups (see Table 14). This analysis gave a significant main effect of **group** ($F(2,74)=3.35$, p = .041) and of **object** ($F(1,74)=7.14$, p = .0092), but not of the group x object interaction ($F(2,74)=1.48$, p = .23). The main effect of object confirms, that it is generally more difficult to detect a luminance change in the moving cursor as opposed to the stationary target.

	Target spontaneous detection threshold (group average in RGB [x,x,x]) (sd)	**Cursor spontaneous detection threshold** (group average in RGB [x,x,x]) (sd)
HC (n=27)	0.50 (0.34)	0.68 (0.27)
OT (n=22)	0.58 (0.32)	0.74 (0.25)
FND (n=28)	0.50 (0.26)	0.52 (0.24)
One-way ANOVA	$F(2,74)=0.54$	$F(2,74)=5.39$
	p = .58	**p = .0066**

Table 15: Target and cursor luminance change spontaneous detection thresholds

As summarised in Table 15, post-hoc one-way ANOVA for the spontaneous detection threshold for the target changing in luminance, gave no significant difference between the three groups. However, one-way ANOVA for the spontaneous detection threshold for the **cursor** changing in luminance, gave a significant effect. Šidák-Holm corrected two sample t-tests showed a significant difference between the FND and the OT groups (p = .0042), and between the FND and the HC (p = .023).

In summary, there is no difference between the three groups in the spontaneous detection of a luminance change of the target. FND patients are significantly better than either control group at detecting a luminance change in the cursor, i.e. in the visual feedback of their movement.

Absolute detection threshold

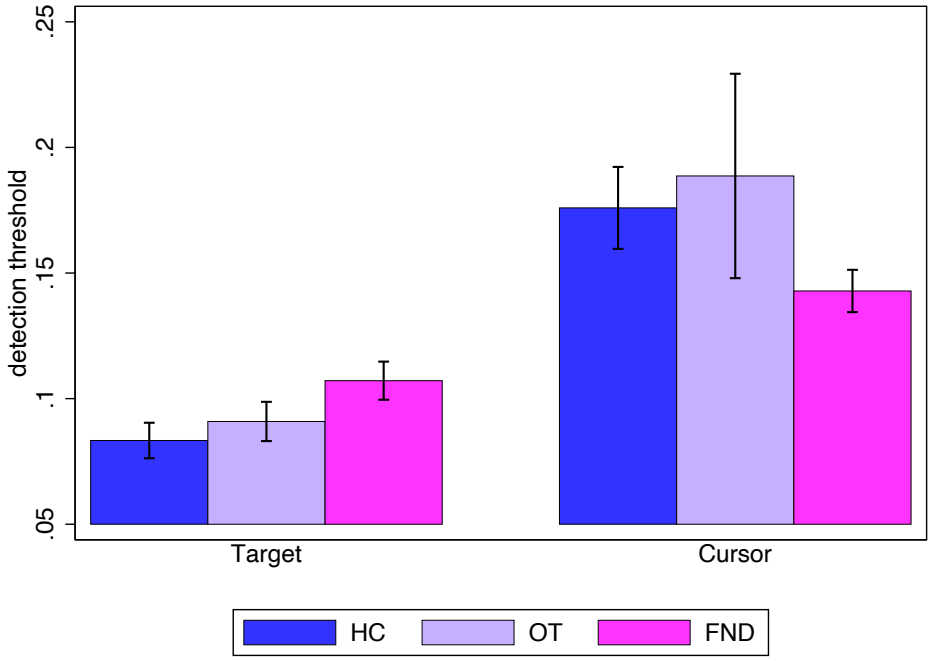


Figure 21: Absolute detection threshold for the target and cursor luminance changes
The standard error of the mean is shown by the error bars.

Since the absolute detection thresholds were not normally distributed for both control groups both for the target and the cursor, and the sample sizes were unequal, the assumptions of the mixed model ANOVA need to be interpreted with some caution (Table 16). It gave a significant main effect of object ($F(1,74)=36.3$) $p < .0001$ confirming again, that it is harder to detect a change in luminance in the moving cursor compared to the stationary target. The main effect of group was not significant ($F(2,74)=0.30$, $p = .74$). There was a trend for the group x object interaction (G-G $F(2,74)=2.64$, $p = .0783$), i.e. looking at Figure 21: Absolute detection threshold for the target and cursor luminance changes there was a trend for the FND group to be worse at detecting a luminance change in the target and better at detecting a luminance change in the cursor compared to the other groups.

	Shapiro-Wilk normality test (p-value)	
	Target **Absolute detection threshold** (group average in RGB [x,x,x])	**Cursor** **absolute detection threshold** (group average in RGB [x,x,x])
HC (n=27)	**0.0023**	**0.00019**
OT (n=22)	**0.028**	**<0.001**
FND (n=28)	0.43	0.72
Levene	p = .88	p = .085

Table 16: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The p-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

A simple Kruskal-Wallis test was performed for the target and the cursor condition separately. This test gave a trend for the target absolute detection threshold, but not for the cursor absolute detection threshold. One-way ANOVAs again need to be interpreted with some caution in view of the non-normal distribution and the unequal sample sizes. Nevertheless, the results corroborated those of the Kruskal-Wallis tests (Table 17).

	Target absolute detection threshold (group average in RGB [x,x,x]) (*sd*)	**Cursor absolute detection threshold** (group average in RGB [x,x,x])(*sd*)
HC (n=27)	0.083 (0.037)	0.18 (0.085)
OT (n=22)	0.091 (0.037)	0.19 (0.19)
FND (n=28)	0.11 (0.040)	0.14 (0.045)
Kruskal-Wallis	$\chi^2(2)=5.98$	$\chi^2(2)=1.71$
	***p* = .0502**	p = .43
One-way ANOVA	$F(2,74)=2.81$	$F(2,74)=1.06$
	***p* = .066**	p = .35

Table 17: Target and cursor luminance change absolute detection thresholds

Two-sample Wilcoxon rank sum tests on the absolute detection thresholds for the target luminance changes, after Holm-Šidák adjustment was significant for the FND versus HC (p = .037) but not for the FND versus OT (p = .094).

In summary, there was a trend for the FND group to be worse at detecting a luminance change of the target when explicitly asked to focus on the target changing in luminance during their reaching movement. The differences in detecting a luminance change of the cursor were not statistically significant.

75% correct detection threshold

Note that the number of subjects within each group were smaller, because the 75% correct detection threshold was only determined in a subset of participants. Practice trials identified the luminance change that lead to an approximately 75% correct detection. However, when evaluating the actual hit percentage (i.e. correct detection) in the *target* condition, this was significantly different from 75% in both control groups (one-sample t-test with a hypothesised mean of 75 HC: $p = .0008$, OT: $p = .0002$). For the FND group, the percent correct detection was not significantly different from 75%. Since percentage of correct detection varies between the three groups in the target condition, the detection thresholds for those percentages cannot be compared to each other.

	Target 75% correct detection threshold (group average in RGB [x,x,x]) (*sd*)	**Cursor 75% correct detection threshold** (group average in RGB [x,x,x]) (*sd*)
HC (n=20)	0.10 (0.047) Hit: 84.6%	0.19 (0.064) Hit (80.6%)
OT (n=22)	0.089 (0.031) Hit: 85.8%	0.17 (0.039) Hit: 81.9%
FND (n=14)	0.089 (0.027) Hit: 76.7%	0.15 (0.052) Hit: 75.5%
One-way ANOVA	**Unequal hits → not comparable**	$F(2,53)=2.81$ $p = .0695$

Table 18: 75% correct detection thresholds for the target and the cursor

For the *cursor* detection thresholds on the other hand, the actual percentage of correct detection was not significantly different from 75% for either group (one-sample t-test with a hypothesised mean of 75 HC: $p = .15$, OT: $p = .13$ and FND: $p = .93$), thus the detection thresholds of the three groups could be compared to each other. A one-way ANOVA (performed in view of the normal distribution in the three groups and the absence of unequal variances), showed a trend to a difference between the three groups, but the Holm-Šidák adjusted two-sample t-tests were not significant for any of the comparisons.

	Shapiro-Wilk normality test (*p*-value)	
	Target 75% correct detection threshold	**Cursor 75% correct detection threshold**
HC (n=20)	0.24	0.63
OT (n=22)	0.24	0.11
FND (n=14)	**0.047**	0.32
Levene	$p = .26$	$p = .29$

Table 19: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

In summary, unequal hit rates for the target condition prevented meaningful analysis of the data. For the cursor the thresholds leading to a 75% correct detection did not vary significantly between the three groups.

2.2.3.4 Target versus cursor luminance change

In this condition subjects had to indicate whether the cursor, the target, both or neither of them had changed in luminance while they moved to cursor to the target.

Simply looking at the hit rate, i.e. the percent correct responses, does not take into account each individual´s bias towards saying yes or no. The hit rate might be high, but if the false alarm rate is high too, then these results are in part a reflection of the subject´s bias towards saying yes and not necessarily a reflection of better detection. Signal detection theory offers a solution to this problem: the discriminability index d' ("d prime") is independent of the response bias.

Using a signal detection theory approach, each individual subject´s discriminability index d' was calculated first and then the group averages were computed. Since hit or false alarm rates of 0% or 100% prevent the calculation of d', the commonly accepted method of exchanging 0 for half a false alarm and 100 for 100 minus half a hit was applied.

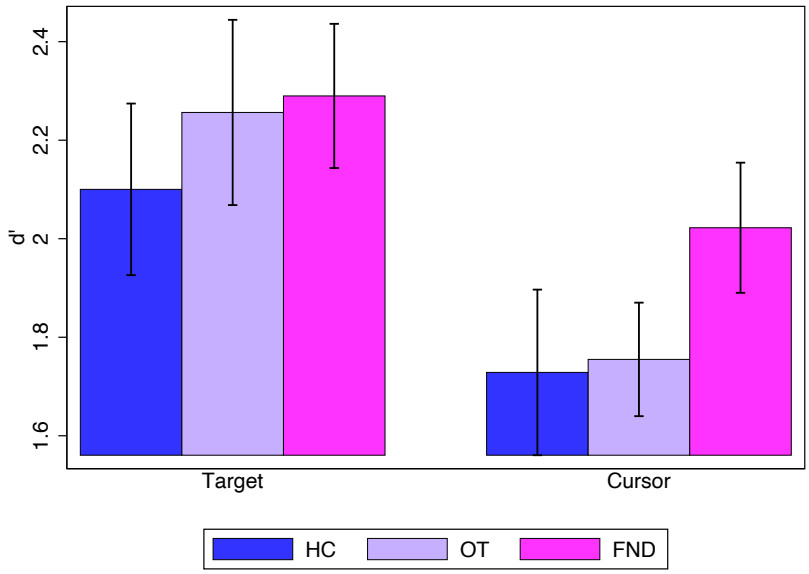


Figure 22: Discriminability index (d') for the target and cursor luminance change
Higher d' indicates higher discriminability, i.e. better sensitivity. The SEM is shown by the error bars.

	Shapiro-Wilk normality test	
	Target d'	**Cursor d'**
HC (n=27)	0.94	0.77
OT (n=22)	0.74	0.83
FND (n=28)	0.84	0.97
Levene	p = .78	p = .31

Table 20: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The p-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

In view of the normal distribution of all the groups and the equal variances (Table 20), a mixed model ANOVA was performed, with group as between-subject factor and object (target versus cursor) as within-subject factor. The main effect of object was significant (G-G, $F(1,74)=8.26$, $p = .0053$), but not the one of group ($F(2,74)=1.39$, $p = .26$), nor the interaction group x object (G-G, $F(2,74)=0.25$, $p = .78$). A one-way ANOVA of the target and cursor d' individually, was not significant for either (Table 21).

	Target	Cursor
	d' discriminability index (group average)	**d'** discriminability index (group average)
HC (n=27)	2.10 (0.91)	1.73 (0.87)
OT (n=22)	2.26 (0.88)	1.76 (0.54)
FND (n=28)	2.29 (0.77)	2.02 (0.70)
One-way ANOVA	$F(2,74)=0.38$	$F(2,74)=1.34$
	$p = .69$	$p = .27$

Table 21: Target and cursor luminance change d'

In summary, a luminance change of the stationary target is overall easier to detect than a luminance change of the moving cursor. There is no statistically significant difference between the groups in the discriminability of the target or the cursor.

2.2.4 Interim discussion

The aim of this study was to establish, where functional tremor patients´ attentional focus natural lies – on the target, the visual feedback of the movement, the proprioceptive-motor aspect of the movement or elsewhere, and if this natural attentional focus differs from the control groups' attentional focus.

The only clear-cut difference in this study was that functional tremor patients were better than either control group at spontaneously detecting that the cursor changed in luminance. The cursor represented the visual feedback of their movement. Thus, this finding suggests that functional tremor patients preferentially focus their attention on the visual feedback of their movement.

This finding is partly corroborated by the fact that more FND patients than healthy controls, but not than organic controls, noticed that the cursor had changed in size. Similarly, in the spontaneous detection of an added deviation, functional tremor patients performed worse than healthy controls, but the difference with the organic tremor group failed to reach statistical significance. Remember, that when the visual feedback is distorted by an added deviation, subjects automatically adjust their trajectory so that the resulting visual feedback is a straight line. A strong attentional focus on the visual feedback would predict a worse performance on the detection of an added deviation, because the proprioceptive information would need to be highly discrepant to signal that it differed from the visual feedback.

For the conditions looking at attention to the target, there was no clear difference between the groups, neither for the detection of a target jump nor for a change in target luminance.

Finally, when directly comparing the sensitivity to a target versus a cursor luminance change by means of a signal detection theory approach, the seemingly improved detection of the cursor in the FND group failed to reach statistical significance.

The question is which test is the best at detecting the natural attentional focus. In a way, the spontaneous detection threshold is the most reliable, because the movement and its attentional focus is not being modified in any way. Its only downside is that subjects sometimes did not say when they noticed something change and therefore had to estimate in retrospect how many times they had noticed it without having said anything. As already discussed, the absolute and 75% correct detection thresholds are more of a measure of how well subjects are able to shift their attention to the required aspect of their movement. If this comes very unnatural to them, they might struggle to shift their attention and naturally drift back to their natural focus, but overall it is not an ideal measure of their natural focus of attention.

The signal detection approach is in theory the best method as long as it does not interfere in the natural attentional focus. Even though subjects were instructed to perform their movement as if there was nothing to look out for, subjects knew that the cursor and the target could change in brightness and so they tended to change their natural attentional focus and try to focus on both the cursor and the target or to switch between the two.

Thus, none of the applied methods is perfect, but overall, the most reliable at detecting the natural attentional focus is the spontaneous detection threshold, which indicated that patients with functional tremor preferentially focus on the visual feedback of their movement.

The absolute and 75% correct thresholds (for an added deviation, a target jump and a cursor luminance change) are not significantly different between the groups, showing that patients with FND are able to shift their attention if required. This is a good and required prerequisite for possible treatments.

The fact that functional tremor patients were better than either control group at spontaneously detecting a change in the cursor excluded the possibility of their attention being generally impaired, or entirely occupied elsewhere, for example on the actual movements.

2.3 Effects of attentional manipulations

A major question is whether a misdirected focus of attention is simply an epiphenomenon, or whether it is in part causative in symptom generation. The effects of different attentional foci on tremor severity were therefore be evaluated.

The aim was to transiently imitate characteristics of functional movement disorders in controls, and conversely to improve functional symptoms in affected patients by certain attentional manipulations. If functional characteristics can be induced or improved in this way, then a causative mechanism of misdirected attentional focus could be implied and these specific attentional manipulations could offer an effective treatment strategy for functional movement disorders.

The initial hypothesis was that the more patients with a functional tremor focus on their movement, the worse their tremor becomes (increase in path length, slowing down of the movement) and the less control they feel over it (decreased sense of agency). The less they focus on their movement (by instead focusing on the goal, something beyond the goal or something unrelated) the more their tremor improves and the more they feel in control. Changing their misdirected focus of attention away from the movement might therefore lead to a near normalisation of their movement disorder.

It was further hypothesised that organic tremor patients can be "made functional" if their attention is manipulated onto the movement. Healthy controls probably show a slight worsening of their movement performance when they focus on their movement, but this might not be marked enough to be detected by the measures used (it is unlikely to induce a tremor, it might, however, slow down their movement and it might decrease their sense of agency)

Overview of attentional manipulations

While the subjects moved their finger from the starting position to the target, their attentional focus was being manipulated in different ways:

- Attention to and away from visual feedback
    - Direct versus indirect visual feedback
    - Absent visual feedback
    - Implicit: detect visual feedback (cursor) luminance change

- Attention to accuracy

- Attention to the movement
    - Implicit: detect if an angular deviation was added to the visual feedback
    - Explicit: told to focus on the movement
    - Slow movement

- Attention to somatosensory feedback

- Attention to the target
    - Implicit: detect target jumping to either side during the reaching movement
    - Implicit: detect target luminance change
    - Explicit: told to focus on the target

- Attention away from the movement
    - Attention beyond the movement
    - Move to the starting point, "just to get ready"
    - Auditory distraction during the movement
    - Fast movement

2.3.1 Overall methods

2.3.1.1 Box on box off

As in the conditions looking at the natural attentional focus (2.2), all the conditions involved a simple reaching movement of the index finger on a touchpad from a starting position to a visual target straight ahead.

The reaching movements were performed under two different overall conditions:

- "Box off" (direct visual feedback) conditions: the subjects' saw both their hand and the touchpad
- "Box on" (indirect visual feedback) conditions: the hand and arm were hidden underneath a horizontal screen onto which the target and current hand positions were projected. This setup removed the direct visual feedback from the hand, and additionally allowed dissociation of visual feedback from proprioceptive-motor information (see below).

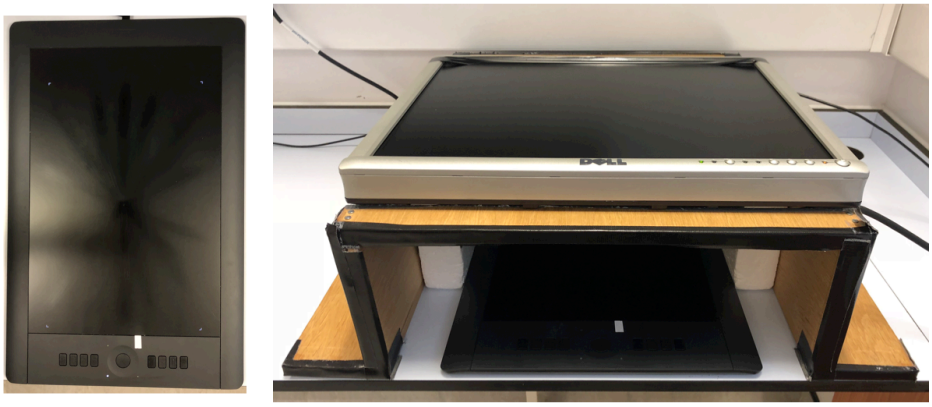


Figure 23: Box off and box on setups
In the box on condition, the subject´s hand and the touchpad on which the finger was moved were hidden underneath a horizontal screen onto which the start, target and the current finger positions were projected in real time.

The location of the finger on the touchpad was recorded every 16ms.

Baseline trajectories

In the baseline conditions, no particular instructions were given so as not to manipulate the subjects' attentional focus in any way. The participants were simply asked to slide their finger from the starting position to the target in one straight movement, without lifting their finger off the touchpad and at a comfortable speed. (Figure 24)

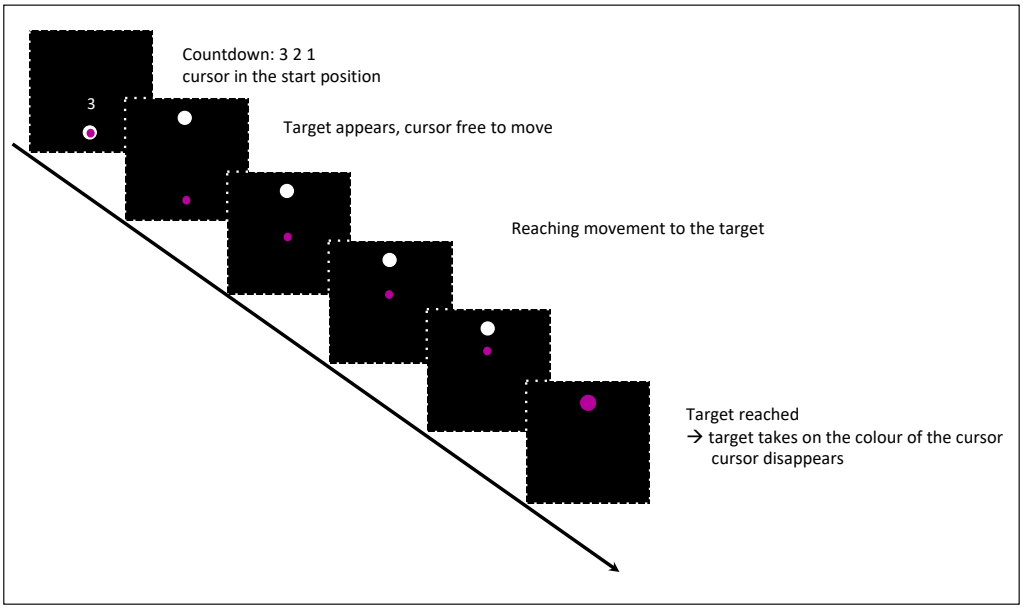


Figure 24: Baseline condition box on

The baseline condition was performed both with and without the box so as to provide the respective baseline for the box on and box off conditions (see below).

2.3.1.2 Analysis of tremor severity: path length and duration

The severity of the tremor was measured by the length of the trajectory drawn on the touchpad (path length in pixels, 10 pixels correspond to approximately 3mm). Another measure of the performance of the movement was its duration (measured in milliseconds). The quality of a movement and indeed the severity of a tremor is primarily analysed in terms of its straightness. Its duration or slowness can also contribute to a movement's quality as exemplified by the impairment caused by bradykinesia in Parkinson´s disease. However, the slowing of the movement observed in many of these attentional manipulation conditions, particularly when compared to the baseline condition, could partly be attributed to the increased attentional load imposed by the additional attentional task. The focus was thus primarily on the path length.

Removing initial loops in the wrong direction and excluding trials with back and forth movements

Since in some conditions subjects had to make an upward movement (starting at the bottom of the screen/touchpad and moving upward) and in others a downward movement (starting at the top of the screen/touchpad and moving downward), they sometimes seemed to get confused and move in the wrong direction at the beginning of a trial or in the middle of it. This artificially prolonged the total path length and its duration and so the trials in which the subject moved up and down during a supposedly single one-directional trajectory were highlighted with the help of a Matlab® program and removed. The cutoff for highlighting a trial in which the subject went in the wrong direction at any point along the trajectory was 80 pixels, or 10% of the total direct trajectory. Note that if the subject overshoot the target by less than 80 pixels or zig zagged around it at the end, then these parts were left unchanged. Equally, trials in which the back and forth movement were due to a severe tremor were retained unchanged.

If the subject initially moved in the wrong direction, away from the target, but then returned to the starting area and performed the rest of the trial correctly, then another Matlab® program removed the initial loop in the wrong direction. The cutoff for removing any initial loop in the wrong direction was 40 pixels, or 5% of the total trajectory. A smaller cutoff was chosen than for the back and forth movement, since removing the initial loop in the wrong direction still maintained the actual trial, whereas if the back and forth movement occurred in the middle of the trajectory, then the entire trajectory was removed.

For each condition, outliers (path lengths shorter than 1.5 times the interquartile range below the 1st quartile, or path lengths longer than 1.5 times the interquartile range above the 3rd quartile) were identified and inspected visually. If such a trajectory had the appearance of a clearly abnormal movement compared to the other trials, e.g. if it was prolonged due to an anomaly, such as a large, unusual sideway or back and forth movement, then it was

retained. Only very few trials were removed this way; on average, approximately two to three trials per subject.

Beginning versus end

A potential effect of more marked tremor at the beginning compared to the end, was offset by the randomisation of the conditions (see A 5.1). This also partly mitigated potential effects of having a worse performance at the beginning due to the unfamiliarity with the task. One condition was, however, not randomised: the baseline condition. Either the baseline box on or the baseline box off condition was always performed first, after 6 -15 practice trials. For most subjects, the baseline condition (either box on or box off, depending on which one was the very first condition) was repeated at the very end of the experiment. Thus, whenever available, the baseline averages were a combination of the baseline trials performed at the beginning and the end of the session on the same day.

Two subjects were very tremulous in the very first baseline condition only, and then their tremor remained fairly stable throughout. Thus, in these subjects, the baseline condition was the one performed at the end.

In the box off condition, one healthy control performed the baseline trials at the very end of the session carelessly, so these were excluded.

Shortest direct trajectory

The target circle was of the same size in all the conditions apart from the following:

Box off – the target area that needed to be reached was 75 pixels in diameter. It was difficult to align the shown target on the touchpad (red laser) exactly with the target area that needed to be reached, thus unknown to the subject, the acceptable target area was made slightly bigger. The same applied to the “absent visual feedback” condition, since otherwise it would have been too difficult to reach the small target.

In the box off and the absent visual feedback conditions, the direct distance between the start and the target was thus slightly shorter than in the standard box on conditions. It was in fact 96% of the direct distance between the start and the target in the box on condition (Figure 25).

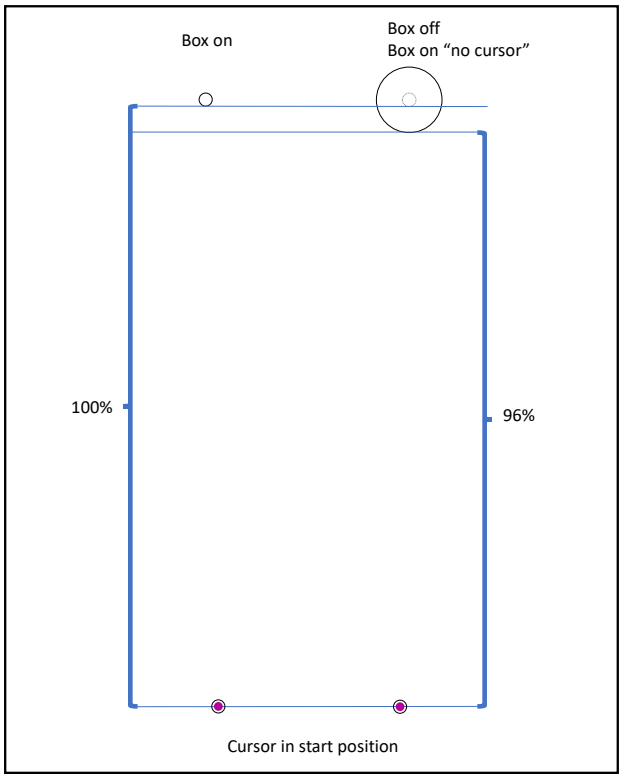


Figure 25: Comparison of target sizes and resulting direct path length
The target was reached, and the trial was over when the centre of the cursor was within the boundary of the target. With the start being centred at -400 pixels and the target (with a diameter of 15 pixels) being centred at 400 pixels, the target was reached after 792.5 pixels (=800-radius of the target) (left part of the figure) (cursor diameter was irrelevant). Right part of the figure: When the target was 75 pixels in diameter, the target was reached after 762.5 pixels, which was 96% of 792.5 pixels. The proportions are respected in this figure.

Hence, whenever all the conditions that were compared were box off conditions, the shortest possible path length was 762 pixels (96% of the shortest path length in a box on condition with target) and the trajectories were analysed up to that level.

Similarly, when the path length or duration of a box off condition was being compared to a box on condition, the path length of the box on condition was only measured up to 96% of the direct path length, so that the minimum direct trajectory was the same as in the box off condition. The possible confounder of a zig zag around the target was an additional reason (see below). When all the conditions that were compared were box on conditions with a normal sized target, then the shortest possible path length was 792 pixels and the entire trajectory was analysed.

- Whenever any condition box off → cut-off 762.5 pixels (96%)
- Whenever all box on and normal sized target present → entire trajectory

Final zig zag as a possible confounder

Subjects often struggled to reach the target (15 pixels diameter) and zigzagged around it right at the end. This obviously prolonged the path length and the duration.

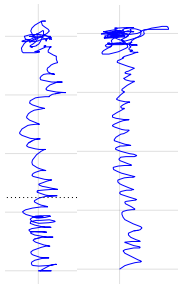


Figure 26: final zigzag in order to reach the target
Two examples of a functional tremor patient showing difficulties to reach the target at the end.

If the conditions being compared all contain a usual sized target (15 pixels diameter) that had to be reached, then the entire trajectories were compared.

- Normal sized target in all conditions → entire trajectory

If on the other hand the target was either an invisible line that needed to be crossed or a larger target (75pixels diameter), then there was no final zig zag around the target and so the very last part of the trajectory, containing the final zig-zag needed to be removed from the comparison condition in which a normal sized target needed to be reached. The final zigzag generally occurred in the last 3-4% of the trajectory, i.e. from 96% onwards. Given 96% was also used for the box off conditions (see above), the same cutoff line was chosen. Thus, for these comparisons, the trajectories up to a line at 96% of the direct trajectory from start to target were analysed

- Whenever box off (larger target) vs box on (normal sized target) → 96% line
- Invisible cursor with larger target versus baseline box on (normal sized target) → 96% line
- Invisible line versus baseline box on (normal sized target) → 96% line

2.3.1.3 Different number of conditions and trials

Not all attentional manipulation conditions were performed by each subject. Some subjects performed all of them, but during two to three different sessions. A baseline condition was performed in every session. Since it is well known, that functional symptoms can vary markedly from one day to the next, only trials performed by a subject on the same day were compared. For obvious reasons, only the subjects that had completed all the conditions of a specific comparison

were included in that analysis. Thus, the number of subjects included in the different attentional manipulation condition comparisons varied. This also precluded the use of more sophisticated models such as linear mixed effects analyses, for comparing conditions performed during different sessions.

For various reasons (fatigue, pain, tremor severity and hence duration of the experiment), some subjects did not perform as many trials within one condition as others. The number of trials per condition are all summarised in appendix A 5.2. The group average for each condition was calculated unweighted, i.e. each subject carried equal weight, regardless of the exact number of trials performed by that subject in that particular condition.

The characteristics of each comparison´s study participants are summarised in A 5.3.

2.3.1.1 Excluded subjects

One of the subjects had a longstanding diagnosis of dystonic tremor, but on examination on the day of the experiment, the tremor was clearly distractible and partly entrainable, indicating a functional component to the tremor. This patient was therefore excluded from all analyses.

Four functional tremor patients were excluded because their tremor was severe at the beginning and gradually improved as time went on, showing a clear linear relationship between time and path length. This clearly represented a strong confounder and so these subjects were excluded from all comparisons over time (attentional manipulation conditions).

Some subjects were more tremulous than others, making them appear to be outliers. They were, however, genuine responses and were therefore not excluded.

2.3.1.2 Statistical analyses

Since the study population comprised patients with different tremor severities, it was unlikely that the path lengths and durations within the tremor patient groups, were going to be normally distributed. Attempts to normalise the data, such as log transformations, or taking the ratio of the two conditions that were being compared did not lead to normalised data. Thus, the raw data was used.

The main question of interest was whether the different attentional manipulations lead to a change of the tremor, i.e. primarily its trajectory length and to a lesser degree its duration, within each group, and particularly in the FND group. The secondary question was whether there was a difference in this response between the groups. Thus, the primary analysis was a paired t-test (or

a Wilcoxon matched pairs signed-rank test in case of non-normality) between the two conditions, for each group separately.

The question of whether there was a difference in the response to the different conditions between the groups was best answered by the interaction term (condition x group) of a mixed model ANOVA. Group was the between-subject factor and condition the within-subject factor. The main effect of condition was of some interest, since it answered the question if there was a difference between the different conditions regardless of group. Nevertheless, it was somehow superfluous in view of the sub-analyses already performed. The main effect of group was of no interest, since the presence of the tremor in the tremor groups as opposed to the healthy controls was expected to lead to longer trajectories. Given the repeated measures design, in case of violations of the assumption of sphericity, the respective *p*-value was adjusted using Greenhouse-Geisser's ε (summarised below as "GG"). Since ANOVA is relatively robust to departures from normality, as long as the variances were not dissimilar and the sample sizes fairly equal, a mixed model ANOVA was performed (Boneau 1960).

2.3.2 Attention to and away from visual feedback

2.3.2.1 Direct versus indirect visual feedback

Methods

As detailed in 2.3.1.1, and in Figure 23, in all the "box off" conditions the reaching movements from the start to the target were performed with the subject seeing both their hand and the touchpad. In all the "Box on" (indirect visual feedback) conditions, the hand and arm were hidden underneath a horizontal screen onto which the starting point, the target and the current hand position were projected.

The baseline conditions with direct and indirect visual feedback were compared, as were two pairs of otherwise identical conditions.

Results

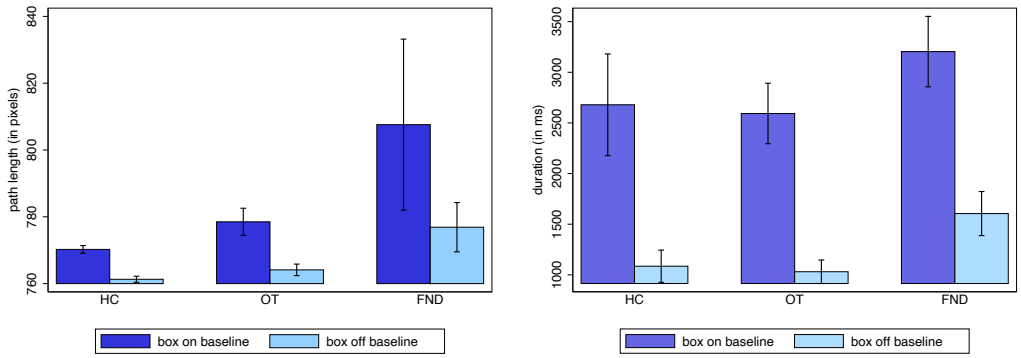


Figure 27: Path lengths of box on versus box off baseline conditions
Path lengths with indirect (box on) and direct (box off) visual feedback for the three groups. The left figure depicts the path lengths, the right the durations. The error bars indicate the standard error of the mean.

The main question of interest was whether there was a difference within each group between the direct and indirect visual feedback conditions. Table 23 summarises the pairwise comparisons between these two conditions for each group (paired t-tests in case of normal distributions, Wilcoxon matched pairs signed-rank test in case of non-normal distributions). All groups had significantly shorter path length with direct compared to indirect visual feedback. The same applied for the durations. Table 22 summarises the tests of normality and equality of variance.

	Shapiro-Wilk normality test (*p*-value)			
	Path length		**Duration**	
	Baseline box **on**	Baseline box **off**	Baseline box **on**	Baseline box **off**
HC (n=20)	0.084	0.63	**<0.0001**	**<0.0001**
OT (n=19)	**<0.0001**	**0.049**	**0.027**	**0.0035**
FND (n=17)	**<0.0001**	**<0.0001**	0.87	0.0599
Levene	***p* = .017**	***p* = .0011**	*p* = .51	*p* = .17

Table 22: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

	Baseline box on	**Baseline box off**	**Paired t-test**	**Wilcoxon signed-rank test**
Path length mean (*sd*) (median) in pixels				
HC (n=20)	770 (5.2) (770)	761 (4.1) (762)	*t*(19) = 8.61, *d* = *1.93* ***p* < .0001**	
OT (n=19)	779 (4.1) (773)	764 (7.5) (764)		*Z* = 3.82, *r* = .88 ***p* = .0001**
FND (n=17)	807 (105.6) (778)	777 (30.4) (766)		*Z* = 2.53, *r* = .61 ***p* = .011**
Duration mean (*sd*) (median) in ms				
HC (n=20)	2679 (2246) (2120)	1085 (711) (1088)		*Z* = 3.88, *r* = .87 ***p* = .0001**
OT (n=19)	2593 (1302) (2283)	1031 (506) (798)		*Z* = 3.82, *r* = .88 ***p* = .0001**
FND (n=17)	3204 (1433) (3005)	1605 (897) (1513)	*t*(16) = 5.11, *d* = *1.24* ***p* = .0001**	

Table 23: Baseline box on versus off
Significant differences are highlighted.

The unequal variances, combined with the absence of normality of the majority of the combinations and the unequal sample sizes, precluded the application of a mixed model ANOVA for the path lengths.

The equal variances between the groups for the durations, on the other hand, allowed the application of a mixed model ANOVA with group as between-subject factor and visual feedback as within subject factor. It showed a significant main effect of visual feedback (direct or indirect) (GG $F(1,53)=71.73$, $p < .0001$) but no significant group x visual feedback interaction (GG $F(2,53)=0.00$, $p = .996$). Thus, it confirmed the duration results of the pairwise tests with all groups grouped together but excluded a difference of this effect between the groups.

Similarly, when checking two further sets of conditions that were performed both with direct and with indirect visual feedback, all three groups had significantly shorter path length with direct visual feedback than with indirect visual feedback. Details of these comparisons, namely explicit attentional focus on the target with direct versus indirect visual feedback and explicit attentional focus on the movement with direct versus indirect visual feedback are available in appendix A 5.4.

In summary, all three groups have significantly shorter path lengths and shorter durations with direct as opposed to indirect visual feedback.

2.3.2.1 Absent visual feedback

Methods

This condition was performed with the box and as soon as the subjects started moving their finger on the touchpad, the cursor (the visual feedback) disappeared.

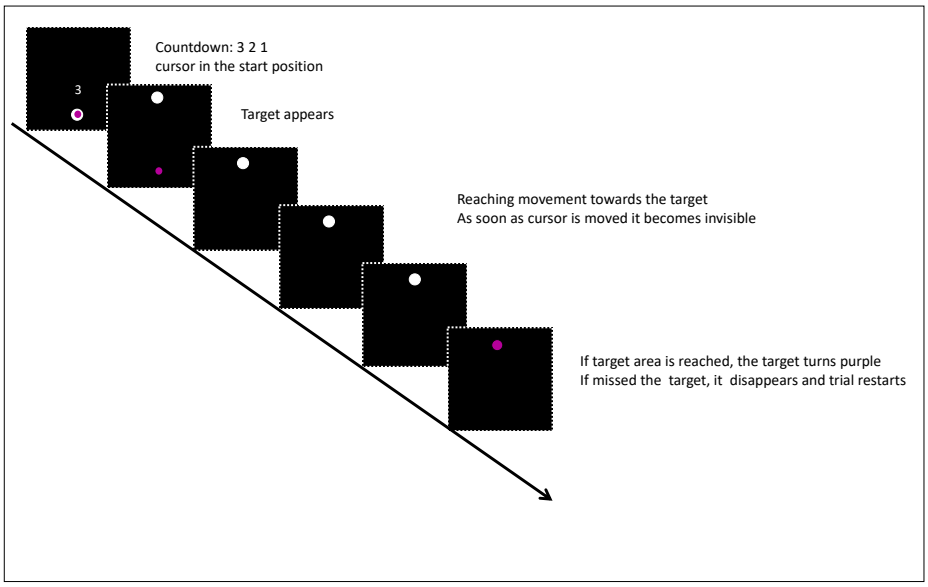


Figure 28: Absent visual feedback condition

Subjects still had to reach the target which appeared in its usual size on the screen, but they were informed that it was larger than in the other conditions (in reality its diameter was 5 times larger (75 instead of 15 pixels)), otherwise the task would have been too difficult (Figure 29). If the target was reached it turned purple and the next trial started, if it was not reached but instead the cursor passed a y threshold beyond the target (100 pixels further), the target remained white and the trial was repeated.

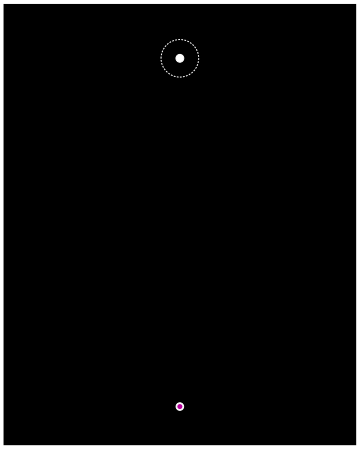


Figure 29: Absent visual feedback
The visible target (white dot) and the acceptable target (dotted circle) sizes are shown at the top and the cursor in the start position at the bottom. The proportions are maintained

Results

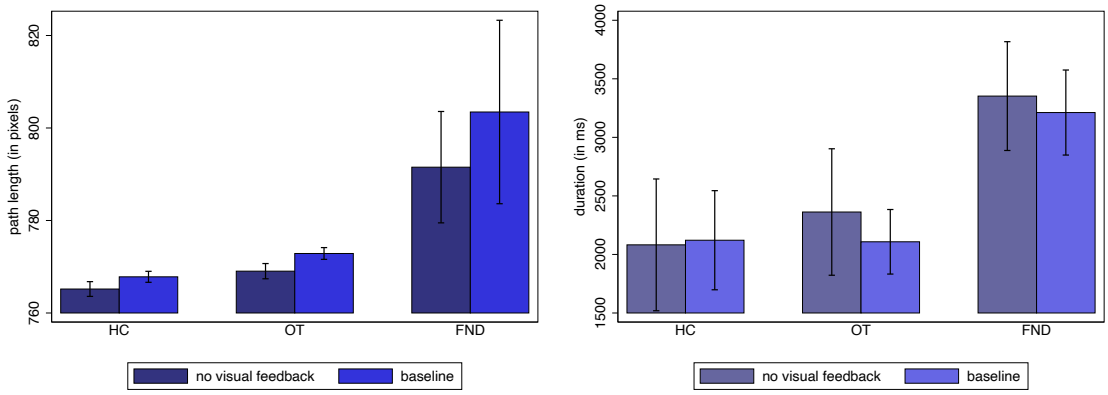


Figure 30: Absent visual feedback versus baseline
The left figure depicts the path lengths, the right the durations. Both conditions were performed with indirect visual feedback. The error bars indicate the standard error of the mean.

As summarised in Table 24, the path lengths were significantly shorter in all groups when there was no visual feedback compared to indirect visual feedback. The durations were not significantly different.

	No visual feedback	**Baseline**	**Paired t-test**	**Wilcoxon signed-rank test**
Path length mean (*sd*) (median) in pixels				
HC (n=23)	765 (7.7) (765)	768 (5.7) (769)	$t(22) = -2.29$, $d = -.48$ ***p* = .032**	
OT (n=18)	769 (7.0) (768)	773 (5.4) (772)	$t(17) = -3.56$, $d = -.84$ ***p* = .0024**	
FND (n=23)	792 (57.7) (775)	803 (95.1) (776)		$Z = -2.55$, $r = -.53$ **p = .011**
Duration mean (*sd*) (median) in ms				
HC (n=23)	2082 (2698) (1362)	2121 (2030) (1398)		$Z = -0.55$, $r = -.11$ $p = .58$
OT (n=18)	2362 (2291) (1814)	2108 (1169) (1676)		$Z = -0.07$, $r = -.02$ $p = .95$
FND (n=23)	3353 (2228) (2397)	3212 (1742) (3005)		$Z = 0.49$, $r = .10$ $p = .63$

Table 24: Absent visual feedback versus baseline

	Shapiro-Wilk normality test (*p*-value)			
	Path length		**Duration**	
	No visual feedback	**Baseline**	**No visual feedback**	**Baseline**
HC (n=23)	.16	.28	**< .0001**	**< .0001**
OT (n=18)	.077	.12	**< .0001**	**.011**
FND (n=23)	**< .0001**	**< .0001**	**.0013**	.053
Levene	***p* = .0064**	***p* = .0069**	*p* = .82	*p* = .55

Table 25: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

The number of subjects having performed the absent visual feedback and the direct visual feedback on the same day was rather small (8HC, 12 OT and 11 FND), thus the results should be interpreted with caution. Nevertheless, the path lengths were significantly shorter in both control groups with direct compared to absent visual feedback, but not in the FND group. The durations were significantly prolonged in both tremor groups. Details are available in annexe A 5.5.

In summary, withholding all visual feedback by hiding the moving limb in a box and not giving any visual feedback in the form of a moving cursor, significantly decreased the length of the trajectory in all three groups, without having any effect on the durations. The number of subjects included in the comparison of direct visual feedback versus no visual feedback were small but did not show any significant difference of the path lengths in patients with FND.

2.3.2.1 Attention to indirect visual feedback

Methods

As the participant reached to the target, the cursor, indicating the current hand position, changed in luminance 0, 1, 2, or 3 times and the subject´s task was to indicate how many times it had changed. Changing from white to grey and back to white counted as one change. This forced the subject to implicitly pay attention to the visual feedback. So as to make the task neither too easy, nor too difficult, the luminance change leading to that subject's 75% correct detection, was first identified and then used. Since the luminance change did not interfere with the movement in any way, all trials were included in the path length and duration analyses.

Results

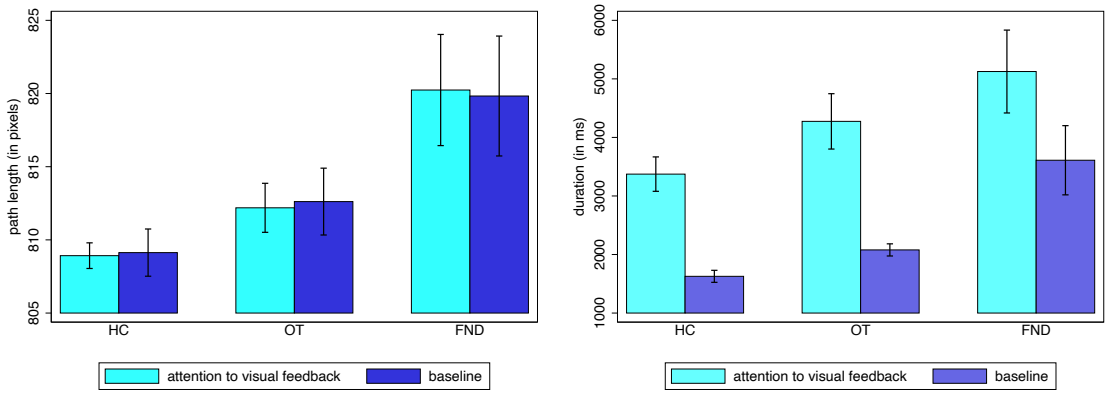


Figure 31: Attention to luminance change of the visual feedback (cursor) versus baseline
The left figure depicts the path lengths, the right the durations. Both conditions were performed with indirect visual feedback. The error bars represent the standard error of the mean.

Given the rounded path lengths were virtually equal in all three groups, there was no indication of performing any statistical tests (see Table 26). The durations were significantly longer in the attention to the visual feedback condition compared to the baseline condition in all three groups.

	Attention to cursor	Baseline	Wilcoxon signed-rank test
Path length mean (*sd*) (median) in pixels			
HC (n=21)	809 (4.0) (810)	809 (7.4) (807)	
OT (n=22)	812 (7.9) (809)	813 (10.7) (809)	
FND (n=13)	820 (13.7) (813)	820 (14.8) (817)	
Duration mean (*sd*) (median) in ms			
HC (n=21)	3373 (1347) (3171)	1627 (471) (1492)	$Z = 3.98$, $r = .87$ **$p = .0001$**
OT (n=22)	4274 (2218) (3536)	2079 (486) (2018)	$Z = 4.11$, $r = .88$ **$p < .0001$**
FND (n=13)	5125 (2552) (4507)	3610 (2131) (2873)	$Z = 2.83$, $r = .79$ **$p = .0046$**

Table 26: Attention to the cursor (visual feedback) versus baseline

	Shapiro-Wilk normality test (*p*-value)			
	Path length		**Duration**	
	Attention to cursor	**Baseline**	**Attention to cursor**	**Baseline**
HC (n=21)	.68	.35	.40	**.0016**
OT (n=22)	**.028**	**.002**	**.0002**	.94
FND (n=13)	.089	.12	.12	**.004**
Levene	***p* < .0001**	*p* = .15	*p* = .15	***p* = .0003**

Table 27: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

In summary, attention to the visual feedback had no effect on the path length but slowed down the movement.

2.3.2.2 Interim discussion

Direct visual feedback lead to better performance than indirect visual feedback, yet no visual feedback lead to better performance than indirect visual feedback. The number of subjects allowing comparison of direct visual feedback with absent visual feedback were small but seem to indicate that there is no significant difference in terms of path lengths in the FND group. Having to reach a target without any visual feedback is obviously much harder, than with visual feedback, thus one might have expected an added component of stress or increased focus on the movement. Despite this, no visual feedback lead to better performance than indirect visual feedback.

Paying attention to a movement irrelevant aspect of the visual feedback versus simply moving to the target with indirect visual feedback had no effect on the pathlengths.

A possible interpretation of these findings is that being given an indirect visual feedback leads to subjects focusing more on the visual feedback, than when they move naturally with direct visual feedback. Yet, focusing on the indirect visual feedback is detrimental, compared to not having any feedback at all.

Of note, the focus on the visual feedback condition (luminance change) concerned an intrinsic aspect of the feedback which was unrelated to the actual movement. That might indirectly have focused the attention on the movement´s feedback, or it might not have. In particular, it might not have focused the attention on the *quality* of the movement, which is what visual feedback is generally used for.

The condition described next thus asked subjects to focus on the accuracy of their movement.

2.3.3 Attention to accuracy

Methods

Subjects were told and reminded in between trials: *"Really focus on your movement so as to make it as accurate as possible. Make the line as straight as possible from the start all the way to the target.* Note that subjects had direct vision of their hand ("box off condition"), the touchpad and the target, but the only visual feedback they received was their moving hand.

Results

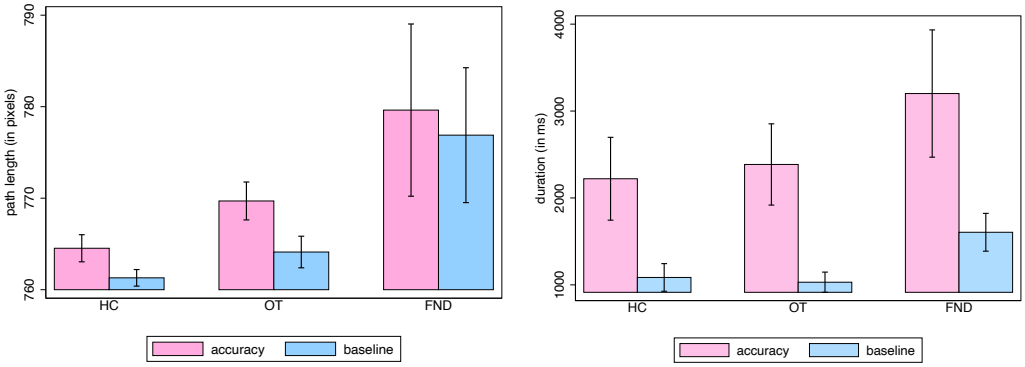


Figure 32: Focus on accuracy versus baseline
Both conditions were performed with direct visual feedback (box off). The left figure depicts the path lengths, the right the durations. The error bars indicate the standard error of the mean.

All groups had significantly longer path lengths and durations when focusing on the accuracy of the movement (see Table 29). In view of unequal variances between groups, non-normal distributions and unequal sample sizes, the assumptions of a mixed model ANOVA were not met for the path length.

	Shapiro-Wilk normality test (*p*-value)			
	Path length		**Duration**	
	Accuracy	**Baseline (box off)**	**Accurate**	**Baseline (box off)**
HC (n=20)	0.25	0.63	**< .0001**	**< .0001**
OT (n=19)	0.062	**0.049**	**0.00077**	**0.0035**
FND (n=17)	**< .0001**	**< .0001**	**< .0001**	0.0599
Levene	***p* = .043**	***p* = .0011**	*p* = .73	*p* = .17

Table 28: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

	Accuracy	Baseline box off	Paired t-test	Wilcoxon signed-rank test
Path length mean (*sd*) (median) in pixels				
HC (n=20)	765 (6.6) (765)	761 (4.1) (762)	$t(19) = 3.09$, $d = 0.69$ **$p = .0060$**	
OT (n=19)	770 (9.0) (767)	764 (7.5) (764)		$Z = 3.30$, $r = .76$ $p = .0010$
FND (n=17)	780 (38.8) (768)	777 (30.4) (766)		$Z = 2.06$, $r = .50$ **$p = .0395$**
Duration mean (*sd*) (median) in ms				
HC (n=20)	2221 (2132) (1609)	1085 (711) (1088)		$Z = 3.47$, $r = .78$ **$p = .0005$**
OT (n=19)	2385 (2037) (1863)	1031 (506) (798)		$Z = 3.70$, $r = .85$ **$p = .0002$**
FND (n=17)	3201 (3019) (2168)	1605 (897) (1513)		$Z = 2.91$, $r = .71$ **$p = .0036$**

Table 29: Focus on accuracy versus baseline

The duration mixed model ANOVA needed to be interpreted with some caution in view of violations of some of its assumptions (normality and unequal sample sizes). It indicated a significant main effect of attentional manipulation (GG $F(1,53)=26.94$, $p< .0001$), but not of the interaction group x attentional manipulation (GG $F(2,53)=0.25$, $p = .78$).

Note that when comparing the accuracy condition to the explicit attention to the movement condition, there was no significant difference between the path lengths. In terms of durations, the healthy controls were significantly slower in the accuracy condition and there was a trend in the same direction for both tremor groups. Details are available in annexe A 5.5.

In summary, focusing on the accuracy of the movement, compared to the baseline condition, led to longer path lengths and durations in all three groups. Compared to explicitly focusing on the movement it did not lead to any significant difference in terms of trajectories.

Interim discussion

These instructions could have several consequences: it could have focused subjects´ attention onto their movement; onto the immediate online outcome of their movement, i.e. the direct visual feedback of their finger; and/or it could have provoked stress since they were told that the line should be as straight as possible. All this said, focusing on accuracy by trying to make the movement as straight as possible led to worse performance in all three groups.

2.3.4 Attention to the movement

2.3.4.1 Implicit attention to proprioceptive-motor information

Methods

Subjects were told that an angular deviation would be added randomly to the feedback of some of their trials and their task was to detect on each trial whether or not there was such an added deviation – "Deviation / no deviation condition" (Figure 33, Figure 34). The amplitude of the added deviation was the amplitude at which the subject had a 75% correct detection rate. Note that there was no visible target in this condition. Subjects were simply told to move up in a straight line and once they had reached the region where the target used to be (once they had crossed an invisible horizontal line that lay at the same y coordinate as the target in the other conditions), a large purple target dot appeared where the cursor had crossed the invisible line. This indicated that the target had been reached and the trial was over.

The acceptable area that needed to be reached was thus much larger. The reason the target dot was removed was to get rid of attention to it. Had the target been present, then subjects would automatically have paid attention to it, by looking at whether they were deviating away from it and ended up to its side or not. Not having the target as a reference point, forced subjects to pay more attention to their actual movement – to the proprioceptive-motor aspect of their movement to be exact, since the visual feedback was being manipulated.

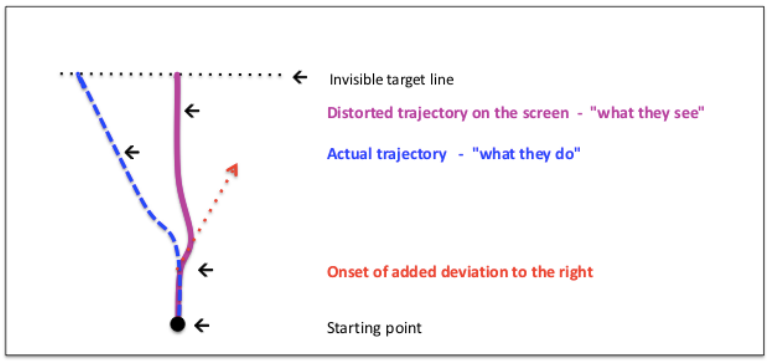


Figure 33: Deviation / no-deviation with invisible target line

Subjects were instructed that the best method was not to try and make the cursor move in as straight a line as possible, since their movement would adapt automatically without them noticing, but instead to concentrate on moving their *finger or arm* in as straight a line as possible.

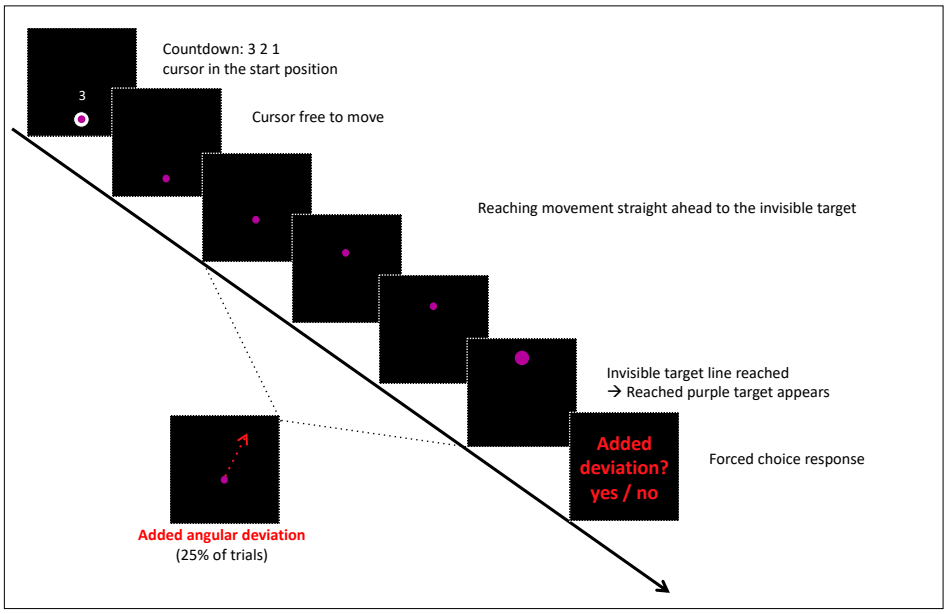


Figure 34: Implicit movement focus condition

Note that only the trials without an added angular deviation were analysed, so as to avoid any confounding effects resulting from movement adjustment.

Results

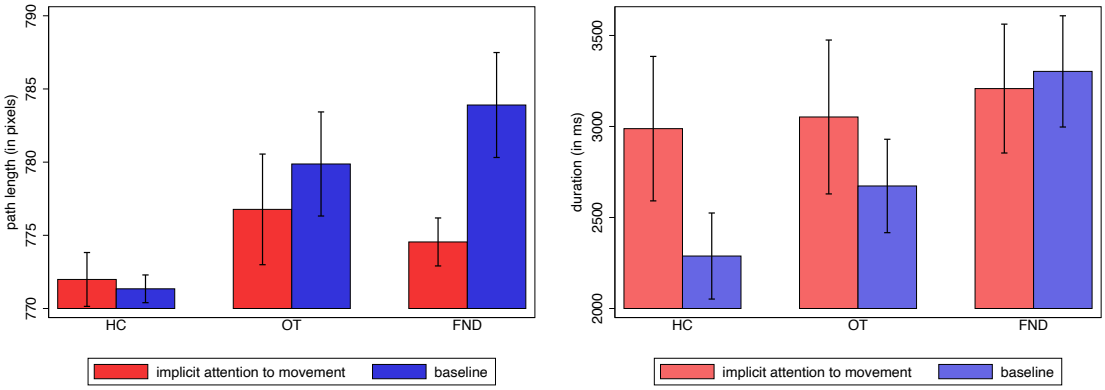


Figure 35: Implicit attention to the proprioceptive aspect of movement versus baseline
The left figure depicts the path lengths, the right the durations. Both conditions were performed with indirect visual feedback. The error bars indicate the standard error of the mean.

As discussed in 2.2.3.1, the actual detection of the added deviation was similar in the three groups, thus the results can be compared to each other. Both tremor groups had significantly shorter trajectories and thus improved tremor when focusing on the proprioceptive-motor aspect of their movement, without having any impact on the speed of the movement. It had no clear effect on the healthy control group, other than slowing down the movement.

For the path lengths a mixed model ANOVA with group as between-subject factor and condition as within-subject factor gave a significant main effect of condition (GG $F(1,62) = 8.04$, $p = .006$) and of the condition x group interaction (GG $F(2,62) = 4.44$, $p = .0158$).

The mixed model ANOVA for the durations was not significant for the main effect of condition (GG $F(1,62) = 2.47$, $p = .12$) nor the group x condition interaction (GG $F(2,62) = 1.23$, $p = .30$).

	Implicit attention to movement	**Baseline**	**Paired t-test**	**Wilcoxon signed-rank test**
Path length mean (*sd*) (median) in pixels				
HC (n=23)	772 (8.8) (771)	771 (4.5) (772)		$Z = -0.09$, $r = -.02$ $p = .93$
OT (n=21)	777 (17.3) (771)	780 (16.3) (776)		$Z = -2.52$, $r = -.55$ **$p = .012$**
FND (n=21)	775 (7.5) (774)	784 (16.4) (781)		$Z = -2.42$, $r = -.53$ **$p = .016$**
Duration mean (*sd*) (median) in ms				
HC (n=23)	2988 (1903) (2208)	2288 (1134) (2282)		$Z = 2.04$, $r = .42$ **$p = .042$**
OT (n=21)	3052 (1937) (2527)	2673 (1176) (2283)		$Z = 0.54$, $r = .12$ $p = .59$
FND (n=21)	3208 (1622) (3094)	3303 (1400) (3005)	$t(20) = -0.29$, $d = -.06$ $p = .77$	

Table 30: Implicit attention to the proprioceptive aspect of the movement (added deviation) versus baseline

	Shapiro-Wilk normality test (*p*-value)			
	Path length		**Duration**	
	Implicit attention to movement	**Baseline**	**Implicit attention to movement**	**Baseline**
HC (n=23)	.20	**.006**	**.004**	**.001**
OT (n=21)	**< .0001**	**< .0001**	**.007**	**.004**
FND (n=21)	.35	**.0001**	.33	.51
Levene	*p* = .23	*p* = .054	*p* = .53	*p* = .18

Table 31: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene´s test of homogeneity of variance in purple. Significant results are in bold.

In summary, focusing on the proprioceptive motor aspect of the movement and while only having a reach a target line instead of a target point lead to shorter path lengths in both tremor groups, without having any impact on the speed of the movement.

2.3.4.2 Explicit attention to the movement

Methods

Subjects were explicitly told and reminded in between individual trials to focus on their movement. Instructions: *"Really focus on your arm or hand movement"*.

This condition was performed both with direct visual feedback (box off) and with indirect visual feedback (box on).

Results

With direct visual feedback (box off)

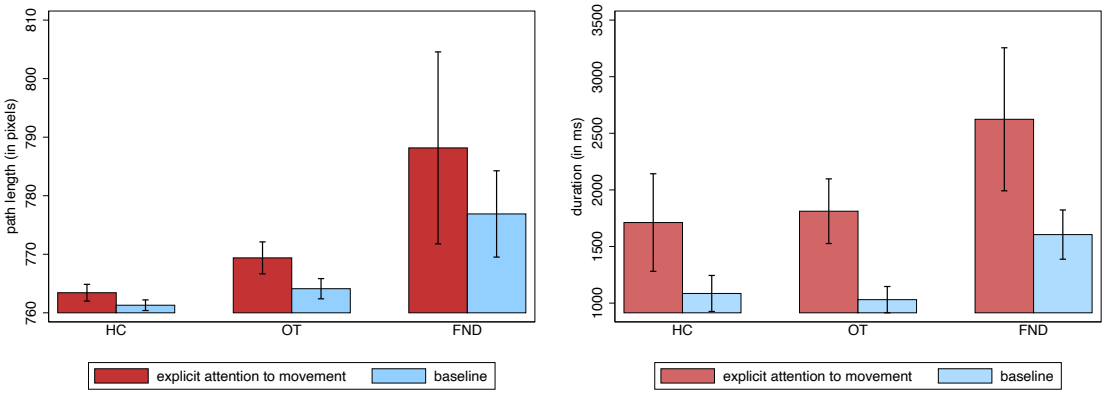


Figure 36: Explicit attention to the movement versus baseline (box off)
The left figure depicts the path lengths, the right the durations. Both conditions were performed with direct visual feedback (box off). The error bars indicate the standard error of the mean.

	Explicit attention to movement	**Baseline box off**	**Paired t-test**	**Wilcoxon signed-rank test**
Path length mean (*sd*) (median) in pixels				
HC (n=20)	763 (6.4) (764)	761 (4.1) (762)	*t*(19) = 2.36, *d = 0.53* ***p* = .029**	
OT (n=19)	769 (11.9) (766)	764 (7.5) (764)		*Z* = 3.54, *r* = .81 ***p* = .0004**
FND (n=17)	788 (67.6) (769)	777 (30.4) (766)		*Z* = 2.25, *r* = .55 ***p* = .025**
Duration mean (*sd*) (median) in ms				
HC (n=20)	1712 (1928) (1441)	1085 (711) (1088)		*Z* = 3.02, *r* = .68 ***p* = .0025**
OT (n=19)	1812 (1245) (1516)	1031 (506) (798)		*Z* = 3.74, *r* = .86 ***p* = .0002**
FND (n=17)	2624 (2605) (1995)	1605 (897) (1513)		*Z* = 2.2, *r* = .53 ***p* = .028**

Table 32: Explicit attention to the movement versus baseline (box off)

With *direct visual feedback*, explicitly paying attention to one´s movement compared to the baseline condition led to significantly longer path lengths and durations in all three groups. (see Table 32).

	Shapiro-Wilk normality test (*p*-value)			
	Path length		**Duration**	
	Explicit attention to movement	**Baseline (box off)**	**Explicit attention to movement**	**Baseline (box off)**
HC (n=20)	.080	.63	**< .0001**	**< .0001**
OT (n=19)	**.0007**	**.049**	**.0041**	**.0035**
FND (n=17)	**< .0001**	**< .0001**	**< .0001**	.0599
Levene	***p* = .021**	***p* = .0011**	*p* = .43	*p* = .17

Table 33: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

With indirect visual feedback (box on)

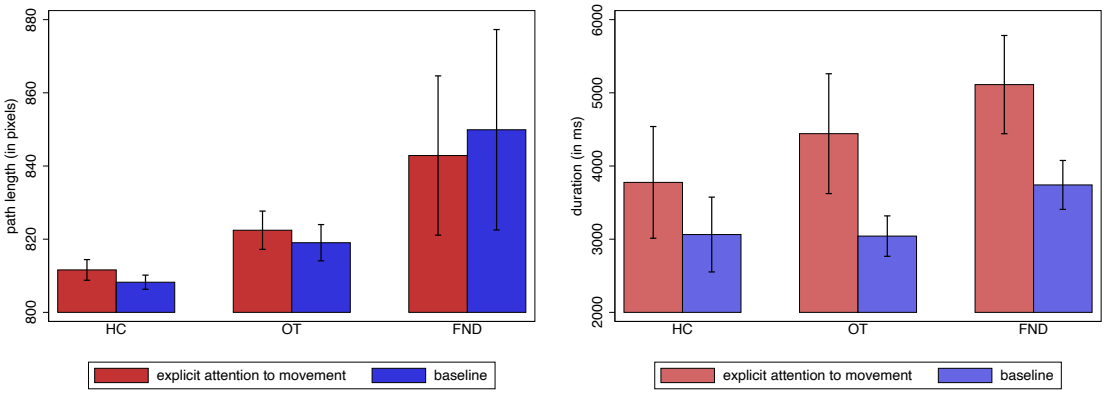


Figure 37: Explicit attention to the movement versus baseline (box on)
The left figure depicts the path lengths, the right the durations. Both conditions were performed with indirect visual feedback. The error bars indicate the standard error of the mean.

With *indirect visual feedback,* explicitly paying attention to one´s movement compared to the baseline condition does not lead to any significant difference in path lengths. In both tremor groups it significantly slows down the movement (see Table 34).

	Explicit attention to movement	Baseline Box on	Paired t-test	Wilcoxon signed-rank test
Path length mean (*sd*) (median) in pixels				
HC (n=20)	812 (12.6) (807)	808 (8.7) (806)		$Z = 0.86$, $r = .19$ $p = .39$
OT (n=21)	822 (24.0) (816)	819 (22.7) (814)		$Z = 1.27$, $r = .28$ $p = .20$
FND (n=19)	843 (94.9) (818)	850 (119.4) (820)		$Z = -0.52$, $r = -.12$ $p = .60$
Duration mean (*sd*) (median) in ms				
HC (n=20)	3776 (3414) (2937)	3063 (2285) (2440)		$Z = 1.72$, $r = .38$ $p = .086$
OT (n=21)	4442 (3751) (2971)	3042 (1265) (2792)		$Z = 2.49$, $r = .54$ **$p = .013$**
FND (n=19)	5112 (2926) (4294)	3741 (1457) (3316)	$t(18) = 2.15$, $d = 0.49$ **$p = .045$**	

Table 34: Explicit attention to the movement versus baseline (box on)

	Shapiro-Wilk normality test (*p*-value)			
	Path length		**Duration**	
	Explicit attention to movement	**Baseline box on**	**Explicit attention to movement**	**Baseline box on**
HC (n=20)	**.0002**	**.0004**	**< .0001**	**< .0001**
OT (n=21)	**< .0001**	**< .0001**	**< .0001**	.011
FND (n=19)	**< .0001**	**< .0001**	.088	.83
Levene	$p = .059$	**$p = .023$**	$p = .91$	$p = .38$

Table 35: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene´s test of homogeneity of variance in purple. Significant results are in bold.

In summary, with *direct visual feedback*, explicitly paying attention to one´s movement compared to the baseline condition led to significantly longer path lengths and durations in all three groups. With *indirect visual feedback,* on the other hand, these comparisons did not show any significant differences.

2.3.4.1 Slow movement

Methods

Subjects were asked to perform very slow reaching movements with indirect visual feedback (box on). The approximate desired speed was demonstrated.

Results

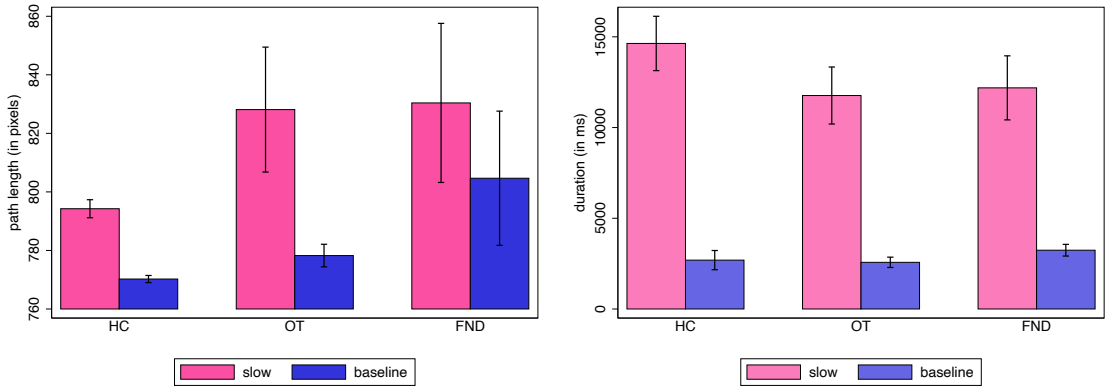


Figure 38: Slow versus baseline
The left figure depicts the path lengths, the right the durations. Both conditions were performed with indirect visual feedback. The error bars indicate the standard error of the mean.

Performing the reaching movement very slowly significantly prolonged the total path length in all subjects compared to the baseline conditions. The significantly prolonged durations confirmed that the task was performed correctly (see Table 36).

	Slow	Baseline	Paired t-test	Wilcoxon signed-rank test
Path length mean (*sd*) (median) in pixels				
HC (n=19)	794 (13.4) (791)	770 (5.3) (771)	$t(18) = 7.74$, $d = 1.78$ $\mathbf{p < .0001}$	
OT (n=20)	828 (95.4) (795)	778 (17.3) (773)		$Z = 3.92$, $r = .88$ $\mathbf{p = .0001}$
FND (n=19)	830 (118.5) 795	805 (99.9) (778)		$Z = 3.06$, $r = .70$ $\mathbf{p = .0022}$
Duration mean (*sd*) (median) in ms				
HC (n=19)	14636 (6528) (14718)	2693 (2307) (2044)		$Z = 3.82$, $r = .88$ $\mathbf{p = .0001}$
OT (n=20)	11765 (7026) (9546)	2572 (1271) (2257)		$Z = 392$, $r = .88$ $\mathbf{p = .0001}$
FND (n=19)	12188 (7695) (8205)	3240 (1403) (3005)		$Z = 3.82$, $r = .88$ $\mathbf{p = .0001}$

Table 36: Slow movement versus baseline

	Shapiro-Wilk normality test (*p*-value)			
	Path length		**Duration**	
	Slow	**Baseline**		**Baseline**
HC (n=19)	.076	.14	.55	**< .0001**
OT (n=20)	**< .0001**	**< .0001**	.0524	**.015**
FND (n=19)	**< .0001**	**< .0001**	**.0002**	.81
Levene	$p = .065$	$\mathbf{p = .028}$	$p = .84$	$p = .36$

Table 37: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene´s test of homogeneity of variance in purple. Significant results are in bold.

2.3.4.2 Interim discussion

Getting subjects attention focused on their movement is difficult, thus it was attempted in different ways. For the explicit attention to the movement conditions, it is impossible to ascertain if subjects followed the instructions and focused on their movement or if they did not. The slowing down of the movement is a positive indicator but it is impossible to be certain. The implicit attentional manipulation condition, in which performing the task correctly automatically focused attention on the correct aspect was thus a better measure than the explicit attentional manipulations.

The results show that having to detect when the visual feedback differed from the performed movement, lead to shorter path lengths in both tremor groups, without having any impact on the speed of the movement. If the visual feedback is distorted by an added deviation to either side and the task is to move in a straight line, the motor system will automatically adjust the trajectory, so that the resulting feedback is a straight line. The easiest way of detecting whether the visual feedback is distorted is by attempting to move in as straight a line as possible and check whether the visual feedback does the same. Indeed, these were the instructions given to the participants; they were told to try to move in as straight a line as possible, almost ignoring the visual feedback. As such, this task forced subjects to focus on their movement, particularly on its proprioceptive motor aspect. However, another technique, applied by some, was to move very quickly, so as not to give the motor system time to correct for the added deviation. Another possible confounding factor is that in the baseline condition, a small target had to be reached, whereas in the implicit attention to the movement condition, an invisible line had to be crossed. It is unclear, how much extra "stress" having to reach a small target had on the entire trajectory. Subjects found it easier not to have to reach a small target, on the other hand, detecting an added deviation was perceived as quite difficult by most subjects, so the overall "stress" levels for the two conditions was likely to be similar. This possible confounding factor could be checked by comparing the trajectories of reaching movements when having to reach a target versus an invisible line, or a large versus a small target. As noted in 2.3.1.2 the final part of the trajectory was removed so as to exclude the zigzagging around the target as a possible confounder.

It was initially hypothesised that focusing on one´s movement would lead to increased tremor and thus path length, but the results show the opposite in both tremor groups. Apart from the possible confounding factors just mentioned, a possible interpretation is that focusing on the proprioceptive aspect of their movement, shifted their attention away from the visual feedback and that this lead to an improvement of their tremor.

It is difficult to explain why explicitly paying attention to one´s movement compared to the baseline condition lead to significantly longer path lengths and durations in all three groups with *direct* visual feedback but had no effect with *indirect* visual feedback. A possible explanation is

that, given their hand and arm were hidden by the box in the indirect visual feedback condition, participants might have struggled to focus on the movement of their limb and instead used the given visual feedback, the cursor as a proxy of their movement and focused on it instead. Alternatively, being given an indirect visual feedback might have led to an increased attentional focus on the indirect visual feedback, making it more difficult to shift the attentional focus to the movement. As alluded to above, the results of the explicit attentional manipulation conditions should be interpreted with caution as there was no way of double checking that the instructions were being followed.

Finally, performing the movement at a very slow speed, required attention to the movement itself and to its visual feedback. It led to significant worsening of the trajectory in all three groups. Note that performing a movement slowly allows a higher number of oscillations to occur during the movement which can also contribute to worse performance. However, since there was also a worsening of the performance in healthy controls, it does not explain the whole picture.

2.3.5 Attention to somatosensory feedback

Methods

Subjects were explicitly told to focus on what their arm felt like as they reached towards the target, on what kind of sensations they perceived in their arm anywhere from shoulder to fingertips. *"Focus on what your arm feels like as you move towards the target"*. After each trial they were asked to report it and the experimenter wrote down the answer. This condition was only performed without the box, so as to maximise the amount of attention that could be paid to the limb.

Results

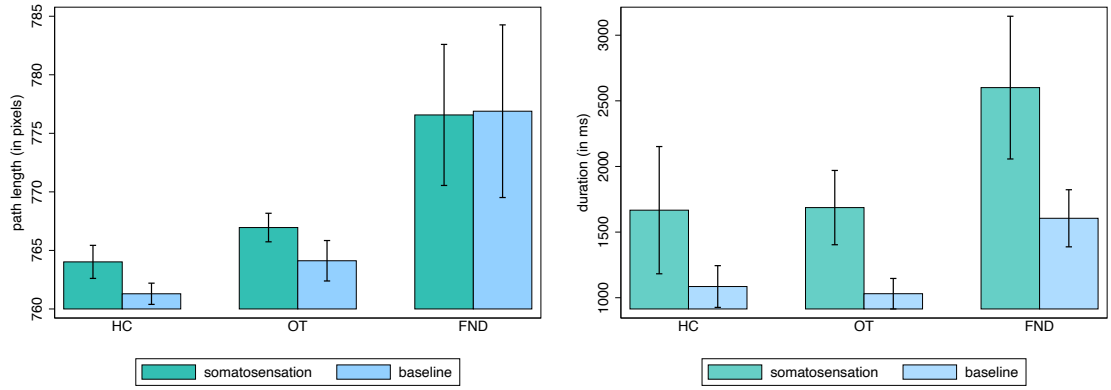


Figure 39: Attention to somatosensory feedback versus baseline
Path lengths are shown in the left figure, durations in the right. Both conditions were performed with direct visual feedback. The error bars indicate the standard error of the mean

As detailed in Table 39 , the trajectories were slightly, but significantly prolonged in both control groups compared to the baseline box off condition, but not in the FND group. The durations were significantly increased in all three groups.

	Shapiro-Wilk normality test (*p*-value)			
	Path length		**Duration**	
	Somato-sensation	**Baseline (box off)**	**Somato-sensation**	**Baseline (box off)**
HC (n=20)	**0.043**	0.63	**< .0001**	**< .0001**
OT (n=19)	0.69	**0.049**	**0.0022**	**0.0035**
FND (n=17)	**< .0001**	**< .0001**	**0.0003**	0.0599
Levene	***p* = .011**	***p* = .0011**	*p* = .55	*p* = .17

Table 38: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

	Somato-sensation	Baseline	Wilcoxon signed-rank test
Path length mean (*sd*) (median) in pixels			
HC (n=20)	764 (6.3) (764)	761 (4.1) (762)	$Z = 2.58$, $r = .58$ **$p = .010$**
OT (n=19)	767 (5.3) (765)	764 (7.5) (764)	$Z = 2.13$, $r = .49$ **$p = .033$**
FND (n=17)	777 (24.8) (770)	777 (30.4) (766)	$Z = 0.88$, $r = .21$ $p = .38$
Duration mean (*sd*) (median) in ms			
HC (n=20)	1667 (2167)	1085 (711) (1088)	$Z = 2.05$, $r = .46$ **$p = .040$**
OT (n=19)	1687 (1234)	1031 (506) (798)	$Z = 3.46$, $r = .79$ **$p = .0005$**
FND (n=17)	2601 (2242)	1605 (897) (1513)	$Z = 2.39$, $r = .58$ **$p = .017$**

Table 39: Somatosensory feedback versus baseline

Interim discussion

Focusing on the somatosensory feedback of the movement, slowed down the movement, and lead to a slight worsening of the trajectory in both the healthy controls and the organic tremor patients. In the patients with FND it only slowed them down, without prolonging the trajectories.

In an attempt to focus on the somatosensory feedback in their arm, the majority of subjects ended up looking at their arm throughout the movement. Since patients with FND might have been focusing on their arm, particularly on its visual feedback anyway, this might explain why this attentional focus did not lead to any worsening.

2.3.6 Attention to the target

2.3.6.1 Implicit target focus condition

2.3.6.1.1 Jump/ no-jump

Methods

In order to direct the subjects´ attention onto the target, they were told, that the target would sometimes randomly jump to the left or right *during* their reaching movement and that their task was to detect if it did.

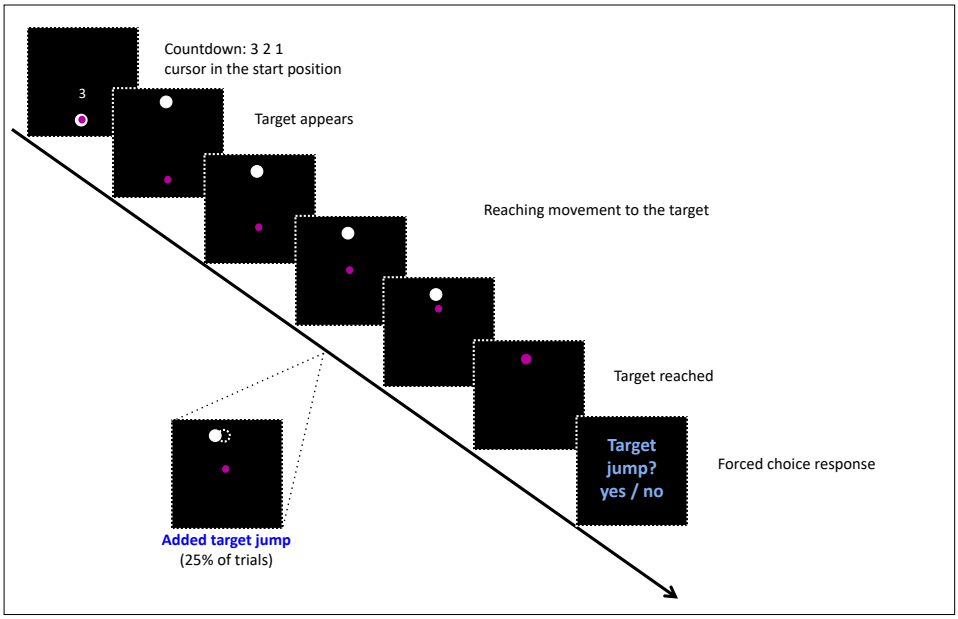


Figure 40: Implicit target focus condition
In 25% of the trials the target randomly jumped to the left or the right once, with an amplitude that previously led to a 75% correct detection. After the movement, the subject indicated whether or not the target had jumped on that particular trial.

Note that this task could only be performed with the box, since the touchpad was not a touchscreen. Only the trials without an added target jump were analysed, so as to avoid any confounding effects resulting from movement adjustment.

As noted in 2.2.3.1, the amplitudes used for this condition were the amplitudes leading to a 75% correct detection in each individual subject. Although numerically slightly higher in the FND group, this slight difference was not statistically significant. Equally, the numerically slightly lower detection rate in the FND group was not significantly different from 75%. Hence this task was well performed by all groups.

Results

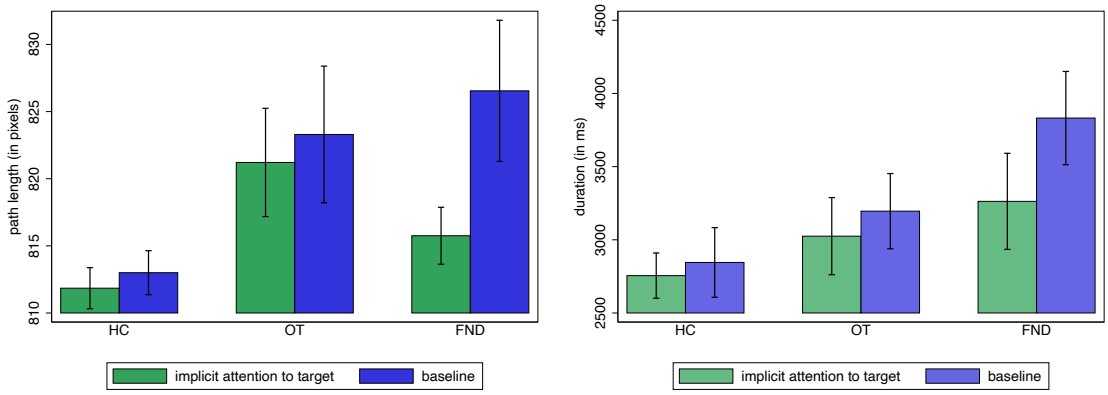


Figure 41: Implicit attention to the target (target jump) versus baseline
The left figure depicts the path lengths, the right the durations. Both conditions were performed with indirect visual feedback. The error bars indicate the standard error of the mean.

Implicitly focusing on the target (focusing on whether it had jumped or not) lead to significantly shorter and faster trajectories in the patients with FND and had no significant effect on either control group (Table 40).

	Implicit attention to target	**Baseline**	**Paired t-test**	**Wilcoxon signed-rank test**
Path length mean (*sd*) (median) in pixels				
HC (n=23)	812 (7.3) (812)	813 (7.9) (811)	$t(22) = -1.13$, $d = -0.24$ $p = .27$	
OT (n=21)	821 (18.5) (815)	823 (23.3) (819)		$Z = -0.61$, $r = -.13$ $p = .54$
FND (n=21)	816 (9.7) (815)	827 (24.1) (821)		$Z = -2.24$, $r = -.49$ **$p = .025$**
Duration mean (*sd*) (median) in ms				
HC (n=23)	2755 (742) (2811)	2845 (1142) (2851)		$Z = 0.27$, $r = .06$ $p = .78$
OT (n=21)	3025 (1208) (2645)	3196 (1178) (2852)		$Z = -1.09$, $r = -.24$ $p = .27$
FND (n=21)	3263 (1505) (3123)	3832 (1460) (3316)	$t(20) = -2.1$, $d = 0.46$ **$p = .0486$**	

Table 40: Implicit attention to the target (target jump) versus baseline

	Shapiro-Wilk normality test (*p*-value)			
	Path length		**Duration**	
	Implicit attention to target	**Baseline**	**Implicit attention to target**	**Baseline**
HC (n=23)	.82	.30	.26	**.004**
OT (n=21)	**.021**	**< 0.0001**	**.002**	**.003**
FND (n=21)	.58	**< 0.0001**	.16	.39
Levene	***p* = .003**	*p* = .0.093	***p* = .023**	*p* = .095

Table 41: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene´s test of homogeneity of variance in purple. Significant results are in bold.

Note that directly comparing implicit attention to the target (jump / no jump) versus implicit attention to the proprioceptive aspect of movement (deviation / no deviation), does not lead to any significant different in path length in any of the groups (HC paired t-test: $t(22) = 0.35$, $d = 0.07$ $p = .73$; Wilcoxon matched pairs signed-rank test OT $Z = 1.48$, $r = .32$, $p = .14$).

2.3.6.1.2 Target luminance change

Methods

As the participant reached to the target, it changed in brightness 0, 1, 2, or 3 times and the subject´s task was to indicate how many times it had changed in brightness. Changing from white to grey and back to white was regarded as one change. This forced the subject to implicitly pay attention to the target. This task was added, so as to allow a direct comparison to the visual feedback luminance change task (see 2.3.2.1).

Results

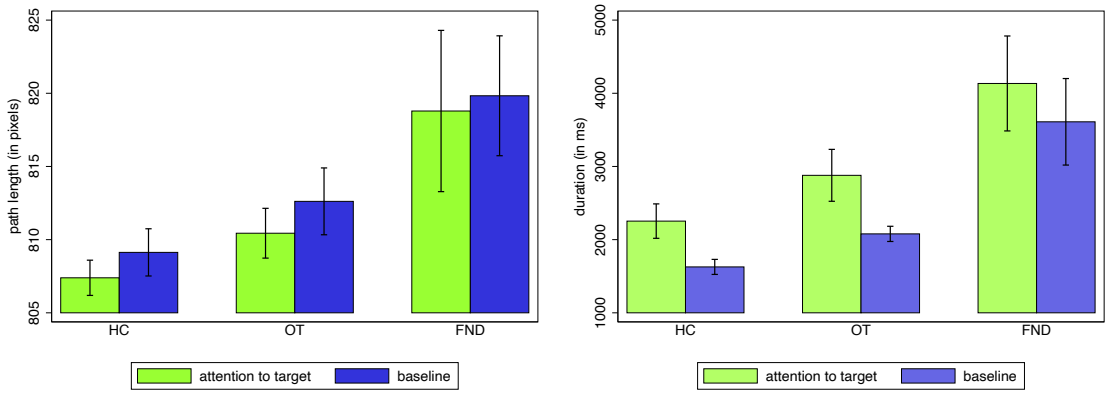


Figure 42: Attention to a luminance change of the target versus baseline
The left figure depicts the path lengths, the right the durations. Both conditions were performed with indirect visual feedback. The error bars indicate the standard error of the mean.

Implicitly focusing on the target by looking out for the number of luminance changes does not lead to any change in trajectory length compared to the baseline condition. It significantly prolongs the duration in both control groups. (Table 42) Note that the number of participants in the FND group is low.

	Target luminance	**Baseline**	**Wilcoxon signed-rank test**
Path length mean (*sd*) (median) in pixels			
HC (n=21)	807 (5.5) (806)	809 (7.4) (807)	Z = -1.06, r = -.23 p = .29
OT (n=22)	810 (8.0) (809)	813 (10.7) (809)	Z = -1.35, r = -.29 p = .18
FND (n=13)	819 (19.9) (811)	820 (14.8) (817)	Z = -0.66, r = -.18 p = .51
Duration mean (*sd*) (median) in ms			
HC (n=21)	2253 (1078) (1878)	1627 (471) (1492)	Z = 3.08, r = .67 **p = .0021**
OT (n=22)	2879 (1664) (2105)	2079 (486) (2018)	Z = 2.74, r = .58 **p = .0061**
FND (n=13)	4134 (2339) (3301)	3610 (2131) (2873)	Z = 1.43, r = .40 p = .15

Table 42: Implicit attention to the target (luminance change) versus baseline

	Shapiro-Wilk normality test (p-value)			
	Path length		**Duration**	
	Target luminance	**Baseline**	**Target luminance**	**Baseline**
HC (n=21)	**.0044**	.35	**.029**	**.0016**
OT (n=22)	.069	**.002**	**.0003**	.94
FND (n=13)	**.0018**	.12	**.025**	**.004**
Levene	**p = .0006**	p = .15	**p = .026**	**p = .0003**

Table 43: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The p-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene´s test of homogeneity of variance in purple. Significant results are in bold.

Cursor versus target luminance change

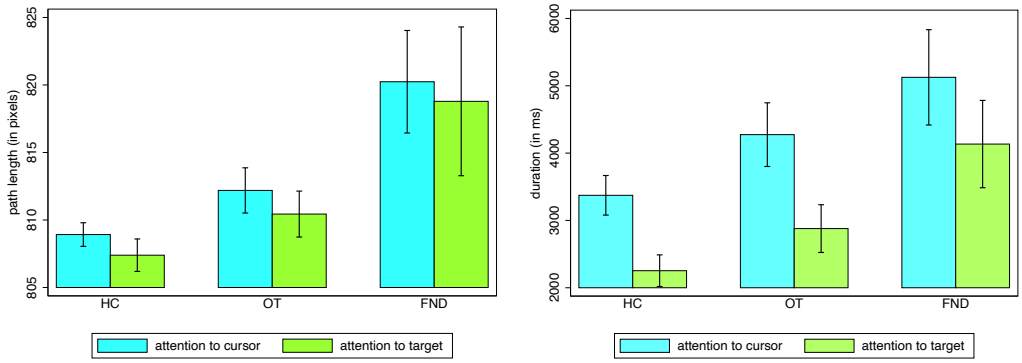


Figure 43: Attention to a luminance change of the cursor versus the target
The left figure depicts the path lengths, the right the durations. Both conditions were performed with indirect visual feedback. The error bars indicate the standard error of the mean.

There was a trend for longer path length in both control groups when implicitly focusing on the cursor as opposed to the target. The durations were significantly prolonged in all three groups when focusing on a change in luminance in the cursor as opposed to the target. It is important to note that the number of patients in the FND group was rather low.

	Cursor luminance	**Target luminance**	**Wilcoxon signed-rank test**
Path length mean (*sd*) (median) in pixels			
HC (n=21)	809 (4.0) (810)	807 (5.5) (806)	$Z = 1.76$, $r = .38$ $\mathbf{p = .079}$
OT (n=22)	812 (7.9) (809)	810 (8.0) (809)	$Z = 1.93$, $r = .41$ $\mathbf{p = .053}$
FND (n=13)	820 (13.7) (813)	819 (811) (19.9)	$Z = 1.15$, $r = .32$ $p = .25$
Duration mean (*sd*) (median) in ms			
HC (n=21)	3373 (1347) (3171)	2253 (1078) (1878)	$Z = 4.01$, $r = .88$ $\mathbf{p = .0001}$
OT (n=22)	4274 (2218) (3536)	2879 (1664) (2105)	$Z = 4.01$, $r = .85$ $\mathbf{p = .0.0001}$
FND (n=13)	5125 (2552) (4507)	4134 (2339) (3301)	$Z = 3.18$, $r = .88$ $\mathbf{p = .0015}$

Table 44: Implicit attention to the cursor versus the target (luminance change)

	Shapiro-Wilk normality test (*p*-value)			
	Path length		**Duration**	
	Cursor luminance	**Target luminance**	**Cursor luminance**	**Target luminance**
HC (n=21)	.68	**.0044**	.40	**.029**
OT (n=22)	**.028**	.069	**.0002**	**.0003**
FND (n=13)	.089	**.0018**	.12	**.025**
Levene	***p* < .0001**	***p* = .0006**	*p* = .15	***p* = .026**

Table 45: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene´s test of homogeneity of variance in purple. Significant results are in bold.

2.3.6.2 Explicit attention to the target

Methods

Subjects were explicitly told and reminded in between trials to focus on the target. Instructions: *"Really focus on the target"*. This condition was performed both with and without the box: "Explicit target focus box off condition" and "Explicit target focus box on condition".

Results

With direct visual feedback (box off)

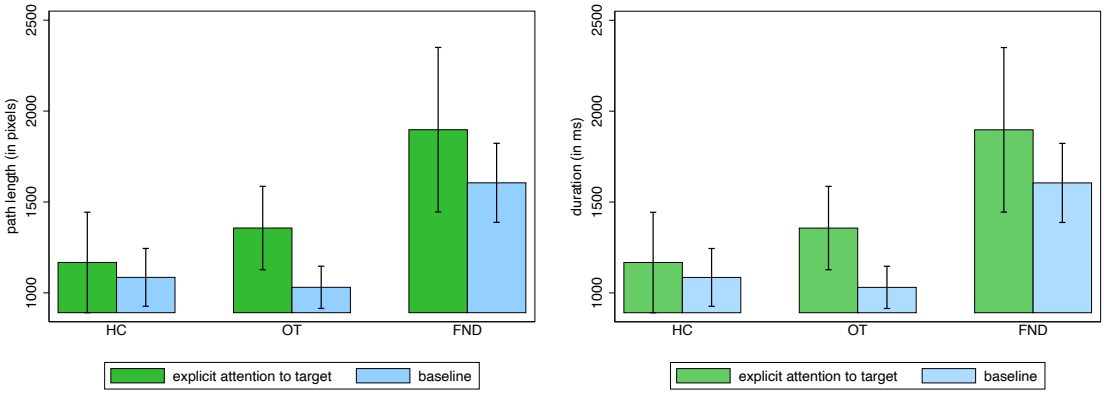


Figure 44: Explicit attention to the target versus baseline (box off)
The left figure depicts the path lengths, the right the durations. Both conditions were performed with indirect visual feedback. The error bars indicate the standard error of the mean.

Explicitly focusing on the target compared to performing the baseline condition had no significant effect on the path length in either group and only significantly prolonged the duration in the organic tremor group (Table 47).

	Shapiro-Wilk normality test (*p*-value)			
	Path length		**Duration**	
	Explicit attention to target	**Baseline (box off)**	**Explicit attention to target**	**Baseline (box off)**
HC (n=20)	0.50	.63	**< .0001**	**< .0001**
OT (n=19)	0.079	**.049**	**0.0024**	**.0035**
FND (n=17)	**0.014**	**< .0001**	**< .0001**	.0599
Levene	***p* = .019**	***p* = .0011**	*p* = .18	*p* = .17

Table 46: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

	Explicit attention to target	**Baseline box off**	**Paired t-test**	**Wilcoxon signed-rank test**
Path length mean (*sd*) (median) in pixels				
HC (n=20)	761 (5.5) (762)	761 (4.1) (762)	*t*(19) = -0.29, *d* =-.06 *p* = .78	
OT (n=19)	765 (10.5) (763)	764 (7.5) (764)		*Z* = 0.89, *r* = .20 *p* = .38
FND (n=17)	771 (15.9) (766)	777 (30.4) (766)		*Z* = -0.83, *r* = .-0.20 *p* = .41
Duration mean (*sd*) (median) in ms				
HC (n=20)	1167 (1236) (860)	1085 (711) (1088)		*Z* = -0.71, *r* = .-0.16 *p* = .48
OT (n=19)	1357 (1000) (844)	1031 (506) (798)		*Z* = 2.01, *r* = .46 ***p* = .044**
FND (n=17)	1897 (1866) (1268)	1605 (897) (1513)		*Z* = 0.02, *r* = .01 *p* = .98

Table 47: Explicit attention to the target versus baseline (direct visual feedback

Explicit attention to the target versus the movement (direct visual feedback)

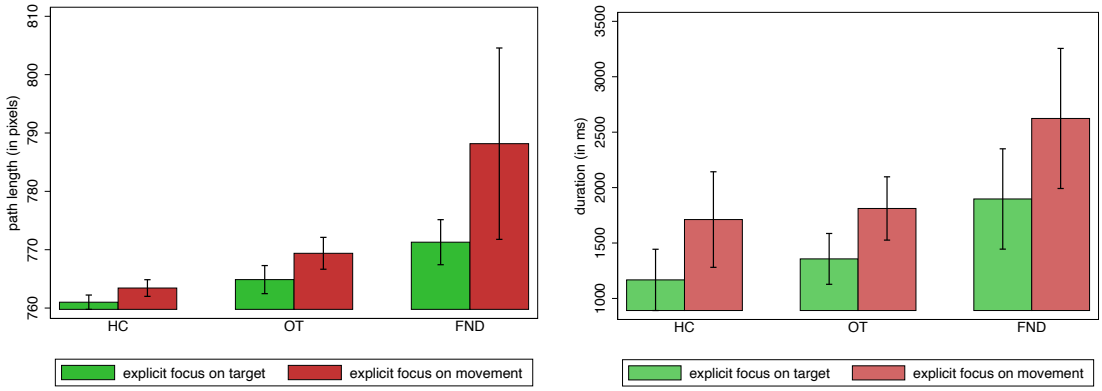


Figure 45: Explicit attentional focus on the target versus the movement

Directly comparing the path lengths in the explicit attention to the target versus the movement conditions showed significantly shorter path lengths and durations in all three groups when explicitly focusing on the target. (Table 48)

	Explicit attention to target	**Explicit attention to movement**	**Paired t-test**	**Wilcoxon signed-rank test**
Path length mean (*sd*) (median) in pixels				
HC (n=20)	761 (5.5) (762)	763 (6.4) (764)	$t(19) = -2.2$, $d = -0.49$ **$p = .041$**	
OT (n=19)	765 (10.5) (763)	769 (11.9) (766)		$Z = -2.98$, $r = -.69$ **$p = .003$**
FND (n=17)	771 (15.9) (766)	788 (67.6) (769)		$Z = -2.77$, $r = -.67$ **$p = .006$**
Duration mean (*sd*) (median) in ms				
HC (n=20)	1167 (1236) (860)	1712 (1928) (1441)		$Z = -3.25$, $r = -.73$ **$p = .001$**
OT (n=19)	1357 (1000) (844)	1812 (1245) (1516)		$Z = 3.3$, $r = -.76$ **$p = .001$**
FND (n=17)	1897 (1866) (1268)	2624 (2605) (1995)		$Z = -2.63$, $r = -.64$ **$p = .009$**

Table 48: Explicit attention to the target versus the movement (direct visual feedback)

	Shapiro-Wilk normality test (*p*-value)			
	Path length		**Duration**	
	Explicit attention to target	**Explicit attention to movement**	**Explicit attention to target**	**Explicit attention to movement**
HC (n=20)	0.50	.080	**< .0001**	**< .0001**
OT (n=19)	0.079	**.0007**	**0.0024**	**.0041**
FND (n=17)	**0.014**	**< .0001**	**< .0001**	**< .0001**
Levene	***p* = .019**	***p* = .021**	*p* = .18	*p* = .43

Table 49: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

With indirect visual feedback (box on)

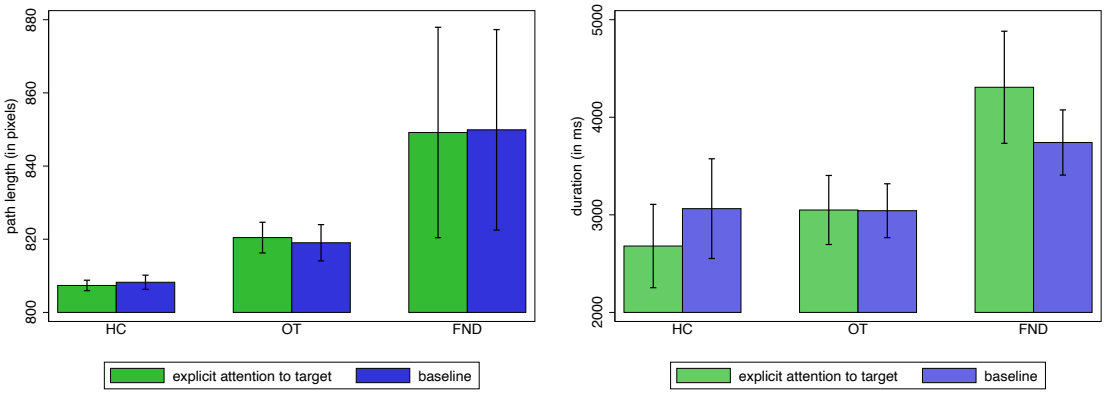


Figure 46: Explicit attention to the target versus baseline (box on)
The left figure depicts the path lengths, the right the durations. Both conditions were performed with indirect visual feedback. The error bars indicate the standard error of the mean.

Explicitly focusing on the target compared to performing the baseline condition with indirect visual feedback had no significant effect on the path length in either group and only significantly prolonged the duration in the healthy control group (Table 50).

	Explicit attention to target	Baseline box on	Paired t-test	Wilcoxon signed-rank test
Path length mean (*sd*) (median) in pixels				
HC (n=20)	807 (6.4) (806)	808 (8.7) (806)		Z = -0.11, r = -.03 p = .91
OT (n=21)	820 (19.2) (817)	819 (22.7) (814)		Z = 0.54, r = .12 p = .59
FND (n=19)	849 (125.3) (813)	850 (119.4) (820)		Z = -0.64, r = -.15 p = .52
Duration mean (*sd*) (median) in ms				
HC (n=20)	2680 (1910) (1969)	3063 (2285) (2440)		Z = -2.24, r = -.50 **p = .025**
OT (n=21)	3050 (1622) (2447)	3042 (1265) (2792)		Z = -0.43, r = -.09 p = .66
FND (n=19)	4307 (2504) (4018)	3741 (1457) (3316)	$t(18)$ = 1.14, d = 0.26 p = .27	

Table 50: Explicit attention to the target versus baseline (indirect visual feedback)

	Shapiro-Wilk normality test (p-value)			
	Path length		**Duration**	
	Explicit attention to target	**Baseline box on**	**Explicit attention to target**	**Baseline box on**
HC (n=20)	**.021**	**.0004**	**< .0001**	**< .0001**
OT (n=21)	**.001**	**< .0001**	**.003**	.011
FND (n=19)	**< .0001**	**< .0001**	.11	.83
Levene	**p = .032**	**p = .023**	p = .094	p = .38

Table 51: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The p-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

Directly comparing the path lengths in the explicit attention to the target versus the movement conditions gave no significant difference in either group (Wilcoxon signed-rank test HC: Z=-1.31, r= -.29, p= .19, OT: Z=-0.68, r= -.15, p= .50, FND: Z= .28, r= .06, p= .78). For details see A 5.7

2.3.6.3 Interim discussion

Two implicit attentional foci on the target conditions were performed. In the first one subjects had to detect whether or not the target had jumped to either side. In the second one the task was to detect how many times the target had changed in luminance. Since a jump of the target affected the trajectory, only trials in which the target did not jump, but in which the attentional focus was nevertheless on the target, were included in the analysis. The change in luminance on the other hand, had no direct effect on the trajectory and thus all trials were included. There might, however, still have been a slight effect on the trajectory when the luminance changed, since some subjects had a tendency to momentarily stop their movement when they noticed a change in luminance. Only analysing the trajectories in which there was no luminance change would lead to too low a number per subject (only 10 instead of 40 trials). Note also, that the number of subjects in the target luminance change condition was rather low in the FND group (13 patients). More weight should therefore be given to the results of the target jump / no jump implicit attentional focus on the target condition.

Explicitly focusing on the target either with or without visual feedback compared to the baseline condition had no significant effect on the path length in either group. Explicitly focusing on the target as opposed to the movement lead to significantly shorter path lengths in all groups with direct visual feedback, but there was no significant difference with indirect visual feedback. As already discussed in the case of the implicit versus explicit attentional focus on the movement, the implicit attentional focus condition should carry more weight as it is impossible to ascertain whether or not the participants were indeed focusing on the target as instructed in the explicit conditions. The performance of the jump or luminance task on the other hand, automatically focused their attention on the target.

A cautious interpretation of the findings is that focusing on the target seems to lead to a mild improvement in the functional tremor group.

2.3.7 Attention away from the movement

2.3.7.1 Attention beyond the movement

Methods

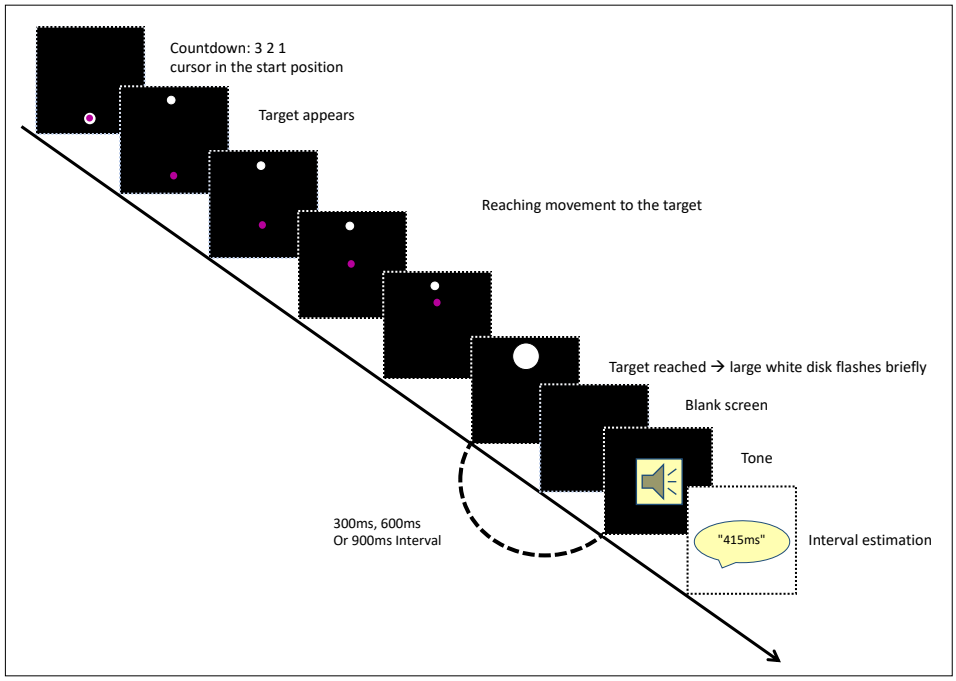


Figure 47: Attentional manipulation beyond the movement condition

This condition was exactly the same as the baseline intentional binding condition described in 3.1.1.2. Subjects were asked to move their finger from a starting position to the target (box on). As soon as they reached the target, a white disk flashed and after an interval of 300, 600 or 900ms a tone sounded. The task was to estimate the interval between the white disk and the tone.

The intention was to shift the subject´s attention to something occurring after the target was reached, in other words the focus of attention lay on something occurring after the movement was completed. Note nevertheless, that the very end of the movement, i.e. reaching the target was a crucial part of the task.

Results

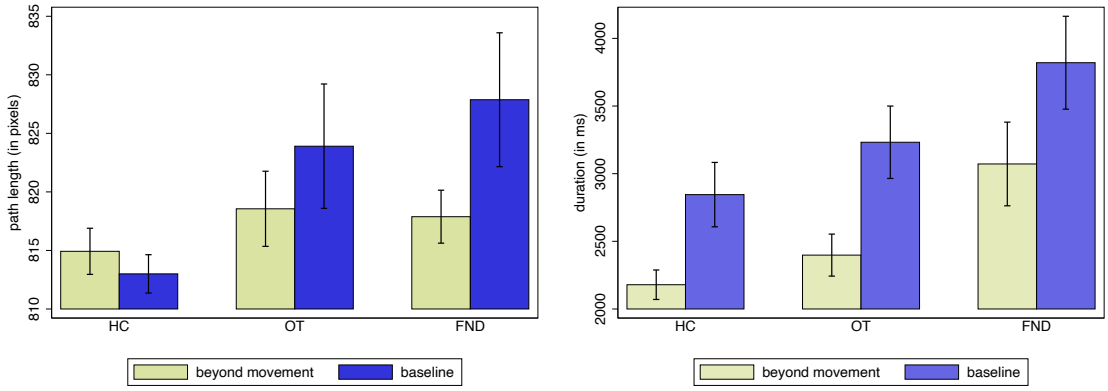


Figure 48: Attention beyond the movement versus baseline
The left figure depicts the path lengths, the right the durations. Both conditions were performed with indirect visual feedback. The error bars indicate the standard error of the mean.

Manipulating the subjects´ attention onto a task occurring after the end of their movement, lead to significantly shorter path lengths in the FND group and significantly slowed down all groups (Table 53).

	Interval estimate	**Baseline**	**Paired t-test**	**Wilcoxon signed-rank test**
Path length mean (*sd*) (median) in pixels				
HC (n=23)	815 (9.4) (813)	813 (7.9) (811)		$Z = 0.46$, $r = .10$ $p = .65$
OT (n=20)	819 (14.4) (817)	824 (23.8) (819)		$Z = -1.64$, $r = -.37$ $p = .10$
FND (n=19)	818 (9.9) (819)	828 (24.9) (822)		$Z = -2.13$, $r = -.49$ $\mathbf{p = .033}$
Duration mean (*sd*) (median) in ms				
HC (n=23)	2179 (523) (2134)	2845 (1142) (2851)		$Z = -3.22$, $r = -.67$ $\mathbf{p = .0013}$
OT (n=20)	2398 (695) (2229)	3232 (1196) (2857)		$Z = -3.77$, $r = -.84$ $\mathbf{p = .0002}$
FND (n=19)	3072 (1348) (3105)	3820 (1497) (3316)	$t(18) = -2.81$, $d = -0.65$ $\mathbf{p = .012}$	

Table 52: Attention beyond the movement versus baseline

For the path lengths, a mixed model-model ANOVA with group as between-subject and condition as between-subject factor gave a significant effect of condition (GG $F(1,59)=4.78$, $p=.033$) and a trend for the group x condition interaction (GG $F(2,59)=2.96$, $p=.0595$).

	Shapiro-Wilk normality test (p-value)			
	Path length		**Duration**	
	Interval estimate	**Baseline**	**Interval estimate**	**Baseline**
HC (n=23)	**.002**	.30	.37	**.004**
OT (n=20)	**.023**	**< .0001**	.33	**.006**
FND (n=19)	**.008**	**< .0001**	.44	.56
Levene	$p = .18$	$p = .076$	$\mathbf{p = .0009}$	$p = .11$

Table 53: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The p-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene´s test of homogeneity of variance in purple. Significant results are in bold.

In summary, manipulating the subjects´ attention onto a task occurring after the end of their movement, lead to significantly shorter path lengths in the FND group.

2.3.7.2 "To start condition"

Methods

In both the target jump/no jump and deviation/no deviation conditions, the movement to the target was preceded by the subject having to move to the starting point first. Subjects were told "it doesn´t count, it´s just to get ready, nothing else". For half the trials they moved from the top to the bottom start position and then back to the target at the top (Figure 49). For the other half the start and the target were inverted, so that the movement to the start was from the bottom of the touchpad / screen to the top. Since all other conditions involved a movement from the bottom of the touchpad to the top, only the upward moving trajectories to the start were included in the analysis. In addition, only the trajectories to the start in the target jump/no jump condition were included. The trajectories to the start in the deviation/no-deviation condition might have been distorted because of adaptation to an added deviation in the previous trial. The movement to the start was nevertheless performed, so that the conditions were otherwise the same between the jump/no-jump and the deviation/no-deviation conditions and so that having to move to the starting point first did not evoke any suspicions.

Its effect was similar to the attentional manipulation beyond the movement condition, in that this condition represented a movement that was of no importance, but simply a means of getting to the actual task.

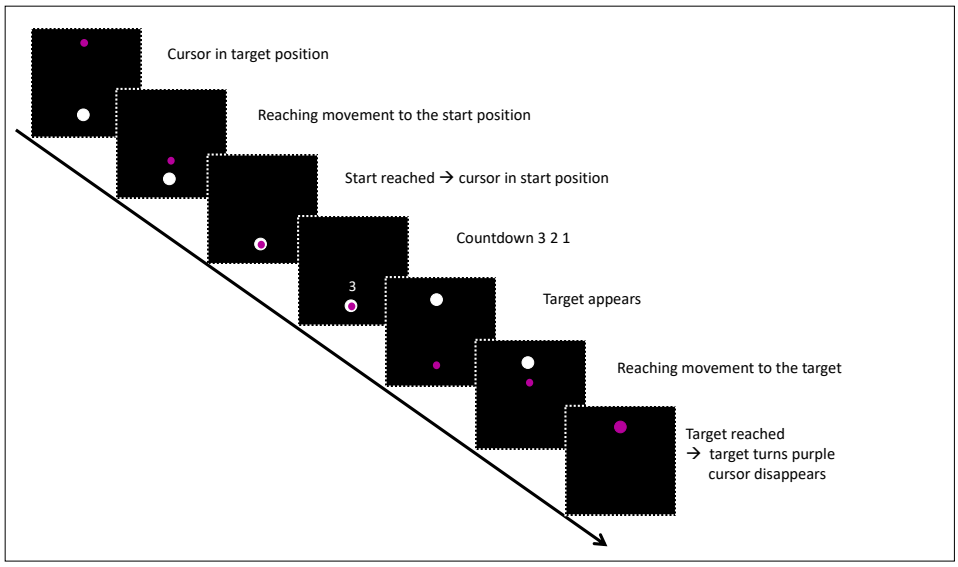


Figure 49: To start condition
The cursor was initially in the target position at the top and subjects were instructed to move it down to the starting position, "just to get ready". Then the countdown appeared, following which they moved to the target. While they moved to the target they were asked to detect if the target jumped to either side (or if a deviation was added respectively) (not depicted in the figure). After half the trials the start and the target were inverted and subjects were told so. Moving to the start thus became the same as the baseline movement to the target.

Results

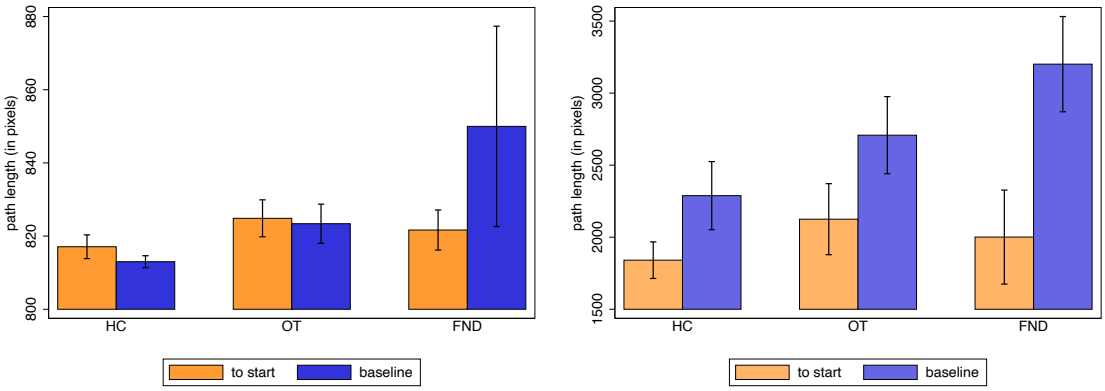


Figure 50: Moving to the start "just to get ready" versus baseline
The left figure depicts the path lengths, the right the durations. Both conditions were performed with indirect visual feedback. The error bars indicate the standard error of the mean.

In the functional tremor group, the path length to the start was significantly shorter than when the same trajectory was performed as a baseline condition. The durations were decreased in all three groups. (Table 54)

The non-normally distributed data with unequal variances and sample sizes between groups did not allow any analysis by a mixed model ANOVA.

	Moving to the start	**Baseline**	**Wilcoxon signed-rank test**
Path length mean (*sd*) (median) in pixels			
HC (n=23)	817 (15.6) (813)	813 (7.9) (811)	$Z = 0.91$, $r = .19$ $p = .36$
OT (n=20)	825 (22.6) (820)	823 (23.9) (818)	$Z = 0.71$, $r = .16$ $p = .48$
FND (n=19)	822 (23.9) (816)	850 (119.4) (820)	$Z = -2.5$, $r = -.57$ **$p = .013$**
Duration mean (*sd*) (median) in ms			
HC (n=23)	1841 (609) (1799)	2288 (1134) (2282)	$Z = -2.46$, $r = -.51$ **$p = .014$**
OT (n=20)	2125 (1102) (1813)	2708 (1198) (2409)	$Z = -2.8$, $r = -.63$ **$p = .005$**
FND (n=19)	2001 (1422) (1508)	3201 (1440) (2873)	$Z = -2.78$, $r = -.64$ **$p = .0006$**

Table 54: Performing the movement as a preparatory movement of no importance ("just move to the start") versus baseline

	Shapiro-Wilk normality test (*p*-value)			
	Path length		**Duration**	
	Moving to the start	**Baseline**	**Moving to the start**	**Baseline**
HC (n=23)	**< .0001**	.30	.10	**.001**
OT (n=20)	.001	**< .0001**	**.006**	**.009**
FND (n=19)	**< .0001**	**< .0001**	**.0005**	.49
Levene	$p = .34$	**$p = .022$**	**$p = .036$**	$p = .25$

Table 55: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene´s test of homogeneity of variance in purple. Significant results are in bold.

In summary, in patients with functional tremor, the path length to the start was significantly shorter than when the same trajectory was performed as a baseline condition.

2.3.7.3 Auditory distraction condition

Methods

While the subject moved their finger to the target, three tones were played. Each one was either high or low pitched. The task was to detect how many of the three tones were high pitched in every trial (Figure 51).

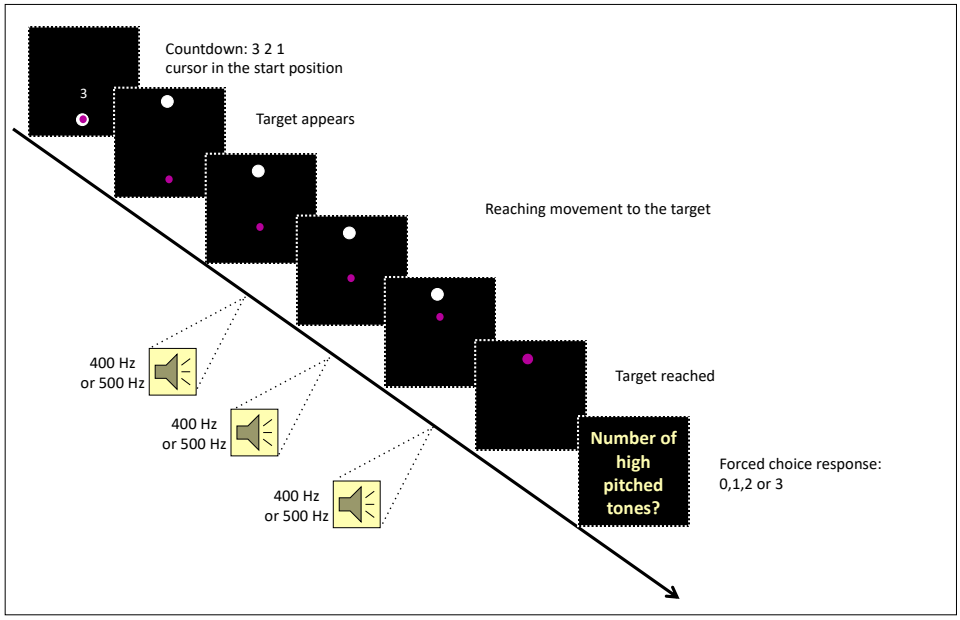


Figure 51: Auditory distraction condition
While the subject moved their finger to the target, three tones were played Each tone was played when a certain y coordinate was crossed, and these thresholds varied slightly in a random fashion from trial to trial. Each tone was either a "low" pitch (400 Hz) or a "high" pitch (500 Hz) tone of 30ms duration. Subjects were shown in advance what was meant by low and high pitch. The answer was given orally and noted by the examiner. This condition was performed with the box.

Results

As detailed in Table 56, all three groups performed the tone identification task well and without significant difference between them.

	Correct detection (group average in %) (*sd*)	False positives (group average in %) (*sd*)	d' discriminability index (Signal detection theory)
HC (n=20)	95.3 (8.7)	2.8 (5.6)	3.93
OT (n=19)	86.7 (20.3)	8.2 (11.1)	3.18
FND (n=17)	88.3 (17.0)	4.6 (7.9)	3.58
One-way ANOVA			$F(2,53) = 1.53$
			$p = .087$

Table 56: Correctly detected high-pitched tones, false alarms and discriminability index

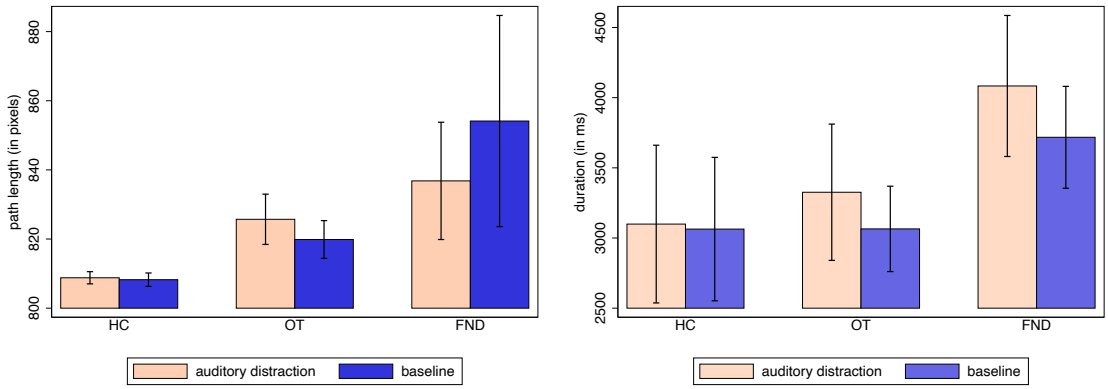


Figure 52: Auditory distraction task versus baseline
The left figure depicts the path lengths, the right the durations. Both conditions were performed with indirect visual feedback. The error bars indicate the standard error of the mean.

Although there is a trend for the path length to decrease in the functional tremor group, this does not reach statistical significance (p= .093, see Table 57)

	Auditory distraction	**Baseline**	**Paired t-test**	**Wilcoxon signed-rank test**
Path length mean (*sd*) (median) in pixels				
HC (n=20)	809 (7.9) (807)	808 (8.7) (806)		Z = 0.52, r = .12 p = .60
OT (n=19)	826 (31.7) 814	820 (23.8) (814)		Z = 0.76, r = .18 p = .44
FND (n=17)	837 (69.9) (819)	854 (125.9) (822)		Z = -1.68, r = -.41 p = .093
Duration mean (*sd*) (median) in ms				
HC (n=20)	3099 (2513) (2512)	3063 (2285) (2440)		Z = 0.71, r = .16 p = .48
OT (n=19)	3326 (2117) (2523)	3065 (1326) (2792)		Z = -0.24, r = -.06 p = .81
FND (n=17)	4083 (2072) (3810)	3718 (1496) (3316)	$t(16)$ = 0.89 , d =0.22 0.22 p = .39	

Table 57: Attention to an auditory distraction task versus baseline

For the path lengths, a mixed model ANOVA with group as between-subject factor and condition as within-subject factor did not give a significant result for the main effect of group (GG $F(1,53) = 0.55$, $p = .46$) nor for the interaction group x condition (GG $F(2,53) = 1.93$, $p = .16$)

For the durations, a mixed model ANOVA with group as between-subject factor and condition as within-subject factor did not give a significant result for the main effect of group (GG $F(1,53) = 1.0$, $p = .32$) nor for the interaction group x condition (GG $F(2,53) = 0.2$, $p = .82$)

	Shapiro-Wilk normality test (p-value)			
	Path length		**Duration**	
	Auditory distraction	**Baseline**	**Auditory distraction**	**Baseline**
HC (n=20)	**.007**	**.0004**	**< .0001**	**< .0001**
OT (n=19)	**< .0001**	**< .0001**	**< .0001**	**.021**
FND (n=17)	**< .0001**	**< .0001**	.40	.90
Levene	$p = .082$	***p* = .017**	$p = .92$	$p = .51$

Table 58: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The p-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene´s test of homogeneity of variance in purple. Significant results are in bold.

In summary, there is only a weak trend for shorter path length with the auditory distraction task in the FND group.

2.3.7.4 Fast movement

Methods

Another way of preventing subjects to pay much attention to their movement, or to let their attention interfere in their movement is to ask them to perform a movement very quickly.

Subjects were therefore asked to do a very quick reaching movement. Of note, they were told that it did not matter if they overshot the target, otherwise they would not have performed it as quickly. The trajectory was therefore only measured up to 96% of the direct path as in many other conditions.

Results

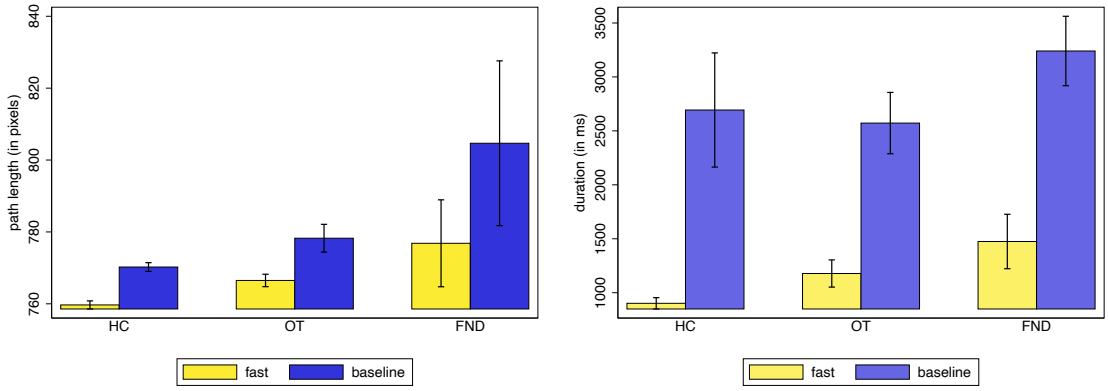


Figure 53: Fast versus baseline
The left figure depicts the path lengths, the right the durations. Both conditions were performed with indirect visual feedback. The error bars indicate the standard error of the mean.

The trajectories were significantly shorter when the movement was performed very quickly, compared to when it was performed as a baseline trajectory. The significantly shorter durations confirmed that the task was performed correctly.

One caveat is that subjects were told that it did not matter if they overshot the target and so they frequently did. While speed improves tremor during the trajectory, the precision at the end is less good.

	Shapiro-Wilk normality test (*p*-value)			
	Path length		**Duration**	
	Fast	**Baseline**	**Fast**	**Baseline**
HC (n=19)	**.036**	.14	.94	**< .0001**
OT (n=20)	.96	**< .0001**	**.016**	**.015**
FND (n=19)	**< .0001**	**< .0001**	**.0006**	.81
Levene	$p = .053$	$\mathbf{p = .028}$	$\mathbf{p = .0009}$	$p = .36$

Table 59: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene´s test of homogeneity of variance in purple. Significant results are in bold.

	Fast	Baseline	Wilcoxon signed-rank test
Path length mean (*sd*) (median) in pixels			
HC (n=19)	760 (4.9) (762)	770 (5.3) (771)	*Z* = -3.78, *r* = -.87 ***p* = .0002**
OT (n=20)	766 (7.7) (766)	778 (17.3) (773)	*Z* = -3.58, *r* = -.80 ***p* = .0003**
FND (n=19)	777 (52.7) (765)	805 (99.9) (778)	*Z* = -3.7, *r* = -.85 ***p* = .0002**
Duration mean (*sd*) (median) in ms			
HC (n=19)	902 (229) (945)	2693 (2307) (2044)	*Z* = -3.7, *r* = -.85 ***p* = .0002**
OT (n=20)	1178 (564) (966)	2572 (1271) (2257)	*Z* = -3.88, *r* = -.87 ***p* = .0001**
FND (n=19)	1475 (1100) (1187)	3240 (1403) (3005)	*Z* = -3.1, *r* = -.71 ***p* = .0019**

Table 60: Fast movement versus baseline

In summary, performing the movement very quickly leads to a straighter trajectory, although the final precision might be impaired.

2.3.7.5 Interim discussion

The aim of these conditions was to distract the subjects' attention away from the actual movement, by giving them the impression that the movement was of no importance: "move to the start just to get ready", "the actual task starts after the movement" (interval estimate), "concentrate on the tones". Or their ability to interfere in the movement was removed by asking them to perform the movement very quickly.

In both the attention beyond the movement condition and the moving to the start condition, patients with functional tremor had significantly straighter trajectories than when they performed the same movement as a baseline condition. Similarly, their trajectories were significantly straighter when they performed the movement very quickly, although the final precision was not improved. The auditory distraction task failed to reach statistical significance, although the trend went in the same direction. Many subjects tended to interrupt their movement whenever they

heard a tone. This might have made the movement less smooth, which might explain why the difference compared to the baseline failed to reach statistical significance.

2.3.8 Interim discussion of effects of different attentional foci

It is well known that distraction improves functional movement disorders, but it is unknown, which exact attentional focus leads to their worsening. Functional tremor patients' attentional focus was thus manipulated onto different aspects of a simple reaching movement and the effects on the tremor were measured. Concomitantly, the effect of different attentional foci on the performance of the reaching movement in patients with an organic tremor and healthy controls were analysed, so as to elucidate whether certain attentional foci could worsen their performance, and hence lead to symptoms resembling functional tremor.

All the attentional foci conditions are listed, with the ones leading to an improvement in tremor (shorter path length) in the FND group highlighted in green, those leading to a worsening highlighted in red and those not leading to any noticeable change compared to a baseline condition without any attentional manipulation in black. Conditions in which this response differed from the organic and healthy control groups are further highlighted by an asterisk.

- Attention to and away from visual feedback:
  - Direct versus **indirect visual feedback**
  - **Absent visual feedback**
  - Implicit: detect visual feedback (cursor) luminance change
- **Attention to accuracy**
- Attention to movement
  - Attention to proprioceptive-motor aspect (target line)
  - Explicit: told to focus on the movement with direct visual feedback
  - Explicit: told to focus on the movement with indirect visual feedback
  - **Slow movement**
- **Attention to somatosensory feedback ***
  - No effect in FND but prolonged paths in both control groups
- Attention to the target:
  - **Implicit: detect target jumping to either side during the reaching movement***
    - no effect in control groups
  - Implicit: detect target luminance change
  - Explicit: told to focus on the target with direct visual feedback
  - Explicit: told to focus on the target with indirect visual feedback
- Attention away from the movement:
  - **Attention beyond the movement ***

        - No effect in HC and OT
    - **Move to the starting point, "just to get ready" ***
        - No effect in HC and OT
    - Auditory distraction during the movement
    - **Fast movement**

Two major themes emerge from these findings: visual feedback and distraction.

Distraction: In the "moving to the start" and in the "beyond the movement" conditions, the movement is thought to be a simple preparatory movement of no importance. As opposed to either control group, patients with a functional tremor perform the movement under those circumstances better (straighter and faster), than when they perform the exact same movement knowing that it is of some importance. One can assume that these movements are performed in a fairly "attention-free" manner. Thus, not giving the movement any importance, not paying attention to it is beneficial in functional tremor. The fact that there is no clear difference between the attention-free and the "attentionful" conditions in either control group seems to indicate that it is not the absence of attention that leads to improvement, but rather that in patients with functional tremor there is something detrimental about the attentional focus during "attentionful" movements. As discussed next, this disadvantageous attentional focus seems to be attention to the visual feedback.

Visual feedback: The findings of the visual feedback and accuracy conditions can be interpreted as indicating that paying attention to the visual feedback of the movement, particularly in terms of its quality is detrimental. The same reasoning might be applied to the results of the attention to somatosensory feedback condition. The reason is that in an attempt to focus on the somatosensory feedback in their arm, the majority of subjects ended up looking at their arm throughout the movement. Since patients with FND might have been focusing on their arm, particularly on its visual feedback anyway, this might explain why this attentional focus did not lead to any worsening in the FND patients but did in both control groups.

The implicit attention to the movement condition contains some possible confounders, namely only having to reach an invisible line instead of a small target and the adoption of different possible strategies in order to complete the task. Nevertheless, since subject were instructed to focus on their movement while ignoring the possibly distorted visual feedback, the shortened trajectories might have been caused by shifting the attentional focus away from the visual feedback onto the proprioceptive motor aspect of the movement.

Performing the movement very slowly lead to worsening and performing it very quickly to improvement in all three groups. A small part of this might be explained by the prolonged time allowing a larger number of oscillations of the tremor to occur in slow movements. Nevertheless,

the speed of the movement by itself could not predict if the trajectories were prolonged or shortened, since different improvements and worsenings of the path lengths with different attentional foci had concomitant shortened, lengthened or unchanged durations. Thus, there is more to a slow or a fast movement than the speed. Performing a movement at an unnaturally slow pace requires attention to the actual movement and probably also its visual feedback, so as to make it slow but at the same time keep it going and prevent it from stopping. When a movement is executed quickly, there is no time for any interference in the movement and so the movement is executed unperturbed. Visual feedback becomes fairly irrelevant for the ongoing movement. Thus, part of the worsening in the slow condition might be due to the effect of attention to the visual feedback and part of the improvement in the fast condition might be due to the absence of attentional focus on the visual feedback with subsequent lack of interference in the movement.

With regards to attentional focus on the target, the results show a significant improvement of the tremor in the FND group in one condition in which the attentional focus was implicitly manipulated onto the target (target jump / no jump condition) but not in the other implicit attentional manipulation condition (target luminance change), nor with an explicit attentional focus. Neither of these conditions had any effect on the path length of the control groups. In the indirect visual feedback conditions, the only task relevant visible objects were the target and the cursor (representing the visual feedback of the finger position). Thus, focusing on the target might have shifted the functional tremor patients´ attention away from the visual feedback onto the target, thereby leading to an improved performance. In the control groups it did not lead to any change in path length, probably because their attention naturally lay on the target. The possible confounding factors in the case of the luminance change conditions have already been discussed (2.3.6.1.2), and the explicit attentional foci condition should not be given too much importance as their correct implementation could not be checked. Nevertheless, given the improvement was only noticed in one of the two implicit attentional foci on the target conditions, the effect might be mild. Focusing on the target might still be too closely related to the movement itself and so prevent patients from shifting the attentional focus away from the movement and its visual feedback. A useful advice is to focus not on the intermediate, but on the ultimate result of the movement. When eating a bowl of peas with a fork for example, focusing on the mouth as the goal of the movement might still make tremor patients focus strongly on their movement. A better strategy might be to focus on the ultimate result of the movement, the taste of the peas for example.

Attention to the different aspects of movement are interlinked and probably often rapidly shifting. As such it is probably impossible to completely separate the different aspects of attention out from each other during a task. Nevertheless, functional tremor patients' natural attentional focus seems to lie on the visual feedback of their movement and indeed, shifting their attention away

from the visual feedback improves their tremor. In parallel, shifting the attentional focus of patients with an organic tremor or of healthy controls onto the visual feedback, particularly on the quality of the movement, leads to slower and shakier movements in a simple reaching task. A misdirected attentional focus on visual feedback therefore does not just seem to be an epiphenomenon but seems to be at least partly causative in symptom generation.

Methodological considerations for the future

Alternative ways of measuring tremor

The initial plan was to test the effect of different attentional foci on the effect of the tremor, the sense of agency and the neural activation pattern. It was postulated that a misdirected focus of attention and indeed a strong attentional focus even during fairly simple movements might be the cause of the frequently observed prefrontal cortical activation in functional imaging studies in FND. The idea was to decrease this abnormal prefrontal cortical activation in functional patients by manipulating their attention away from the movement and conversely to recreate it in healthy or organic controls by manipulating their attention onto the movement. The reaching movement and its measurement therefore needed to be feasible inside an MRI scanner. This is the reason why the fairly simple measurement on a two-dimensional surface was chosen. Three-dimensional measures by means of either a robot or 3D sensors and the addition of an accelerometer could provide more detailed information about the tremor and the effect of different attentional manipulations. Care needs to be taken, that these measuring devices do not interfere in the normal movement or direct the subject´s attention onto the devices or the body parts they're attached to.

EMG

Forceful contraction of antagonistic muscles can lead to tremor in a healthy subject and worsen an existing organic action tremor. In many cases of functional tremor, a co-contraction of antagonist muscles can be seen. Numerous studies in the context of sports show that applying an internal body oriented focus of attention, compared to an external goal directed focus leads to increased muscular activity (Lohse et al. 2010; Vance et al. 2004; Zachry et al. 2005). It can therefore be presumed that attention focused onto one's movement or even its visual feedback while the movement is still ongoing, leads to increased muscular activity and that this can directly contribute to the generation of a tremor. Surface electromyography (EMG) could therefore be measured during different attentional manipulation conditions. In view of the frequently observed co-contraction of agonists and antagonists, ideally an agonist-antagonist pair should be measured.

This was in fact attempted, but the signals from the biceps-triceps were too small and so the anterior and posterior deltoid were chosen. Unfortunately, the resulting traces were suboptimal: the reaching movement involved movement of the entire arm, leading to important artefacts.

Given the anterior and posterior deltoid are to some degree involved in stabilisation of the shoulder, they were activated in both flexion and extension of the shoulder, so there was no clear agonist-antagonist pattern. The anticipated effects of attention on muscle activation are small and thus likely drowned in these artefacts.

EMG recording could be attempted under different attentional manipulation conditions using smaller movements, such as for example wrist movements.

2.4 Patient's perception

In order to allow comparison to the results of the attentional manipulation conditions, the analyses presented here only include the patients who took part in at least some of the attentional manipulation conditions. Annexe A 6 summarises the findings for all patients with a functional movement disorder (including tremor), an organic movement disorder, and all healthy controls.

2.4.1 Attention to movement - Masters' movement specific reinvestment scale

Methods

The Masters' movement specific reinvestment scale (A 2.3 and Table 61) is a ten-item questionnaire testing a person's tendency to conscious monitoring of their movements, their conscious attention to the process of movement (Eves, Maxwell, and Masters 2005). Each of the ten questions is rated on a six-point Likert scale leading to a total score of 10-60 points. It contains two subscales, the conscious motor processing subscale which evaluates the contemplation of the process of movement, and the movement self-consciousness scale, which evaluates the concern about one´s "style" of movement and about making a good impression when moving in public.

Results

As summarised in Table 61, overall movement specific reinvestment scale scores were very similar between the functional and organic tremor groups, and they were both significantly higher than the scores of healthy controls. This also applied to both subscales (the conscious motor processing subscale and the movement self-consciousness sub-scale), and to every single question apart from number 9 which was not significantly different between the three groups ("If I see my reflection in a shop window, I will examine my movements."). The effect size of $\eta^2 = .25$ for the overall score indicated a large effect.

Comparing the scores not just of patient with a tremor but of movement disorder patients of functional and organic origin and healthy controls gave the same overall results. (Details are available in A 6.1)

	Healthy control (n=44) (*sd*)	organic Tremor (n=27) (*sd*)	functional Tremor (n=37) (*sd*)	One-way ANOVA	
Overall score	**20.7** (10.3)	**33.6** (14.2)	**34.8** (11.9)	$F(2,105) = 17.03$ $\eta^2 = .25$	***p* < .0001**
Conscious motor processing sub-score	**11.0** (5.8)	**17.9** (7.6)	**18.5** (7.1)	$F(2,105) = 15.46$ $\eta^2 = .23$	***p* < .0001**
I rarely forget the times when my movements have failed me, however slight the failure.	2.2	3.3	3.4	$F(2,105) = 5.65$	$p = .005$
I am always trying to figure out why my actions failed.	2.2	3.1	3.7	$F(2,105) = 6.81$	$p = .002$
I reflect about my movement a lot.	2.0	3.8	3.8	$F(2,105) = 15.5$	$p < .0001$
I am always trying to think about my movements when I carry them out.	1.5	1.9	2.0	$F(2,105) = 12.39$	$p < .0001$
I am aware of the way my mind and body works when I am carrying out a movement.	2.7	4.1	3.9	$F(2,105) = 6.61$	$p = .002$
Movement self-consciousness sub-score	**9.8** (5.7)	**15.9** (7.3)	**16.3** (6.4)	$F(2,105) = 12.93$ $\eta^2 = .198$	***p* < .0001**
I am self-conscious about the way I look when I am moving.	2.4	3.5	4.1	$F(2,105) = 9.62$	$p = .0001$
I sometimes have the feeling that I am watching myself move.	1.6	3.1	2.8	$F(2,105) = 8.47$	$p = .0004$
I am concerned about my style of moving.	1.8	3.4	3.6	$F(2,105) = 16.68$	$p < .0001$
If I see my reflection in a shop window, I will examine my movements.	2.2	2.2	2.1	$F(2,105) = 0.01$	$p = .99$
I am concerned about what people think about me when I am moving.	1.8	3.7	3.6	$F(2,105) = 16.97$	$p < .0001$

Table 61: Master's movement specific reinvestment scale for the subjects taking part in the attentional manipulation experiments
Overall score, sub-scores for the two subscales, and scores for each individual question, together with the respective one-way ANOVA. The values in brackets give the standard deviation.
(Šidák adjusted post-hoc two-sample t-tests on the total scores were highly significant for the HC compared to either tremor group but not between the two tremor groups (HC versus FND: $p < .001$, HC versus OT: $p < .001$, FND versus OT: $p = .97$). The same applied to the conscious motor processing sub-score (HC versus FND: $p < .001$, HC versus OT: $p < .001$, FND versus OT: $p = .98$) and the movement self-consciousness sub-score (HC versus FND: $p < .001$, HC versus OT: $P < .001$, FND versus OT: $p = .99$)).

Interim discussion

One might have expected functional tremor patients to have very high scores, and healthy controls low ones, with organic tremor patients displaying intermediate scores. However, functional and organic tremor patients score equally high on the Masters´ movement specific reinvestment scale,

both significantly higher than healthy controls. These findings suggest that a tremor or indeed any movement disorder in view of the high scores for all movement disorder patients, regardless of whether they are of organic or functional origin) is sufficient to induce increased attention to the movement, with increased conscious motor processing and increased movement self-consciousness.

In addition, high scores in organic tremor patients might make them more susceptible to developing functional symptoms and it is indeed known that an estimated 10-15% of patients with an organic movement disorder have an additional functional movement disorder and that 12% of patients with a neurological disease also display “symptoms unexplained by the disease” (Ranawaya, Riley, and Lang 1990; Stone et al. 2012).

2.4.2 Attention to good outcome

Methods

The following questions were asked orally:

- Q1: “When you try hard to make a movement perfect or to do something perfectly, do you think it turns out better or worse than if you just did it without much thought?
- Q2: Why do you think that is the case?
- If the response to Q1 was
    - “better”
        - then Q3 was: “Have you ever experienced that your movement was impaired when you tried hard to make it perfect? Even though you were able to do it well when you didn´t think about it? If so, can you give me an example?”
    - “worse”
        - Then Q3 was: “Can you give me an example?”

Results

As can be seen in Table 62, far more patients with either tremor type find that trying hard to make a movement perfect rather than just doing it without much thought makes it worse rather than better. Healthy control subjects on the other hand gave a more balanced response.

	Worse	**Same or it depends**	**Better**
HC (n=24)	41.7%	20.8%	37.5%
OT (n=23)	78.3%	8.7%	13.0%
FND (n=28)	67.9%	21.4%	10.7%
Fisher´s exact test	*p* =.057		

Table 62: Responses to the question: “When you try hard to make a movement perfect, do you think it turns out better or worse than if you just did it without much thought?”
Since some expected frequencies were below 5, Fisher´s exact test was used instead of Pearson´s chi-square test.

Similar results emerge, when including patients with any type of functional or organic movement disorder (see A 6.2).

When asked what they thought the reason for a worsening were, the following themes emerged:

- Overthinking
- Tensing up

- Getting annoyed or irritated
- Less natural
- More attention, concentration
- Fear that the tremor will be severe
- No idea

These are some of the examples given by functional and organic tremor patients and healthy controls:

OT: “Sometimes, I carried a cup without spilling and then realise that I have just done it, and as realise that I start shaking.”

OT: “For example carrying a cup of tea. If I carry it for myself I am more stable than if I carry a cup of coffee for my wife. I’m not thinking about my cup of tea. But when I am carrying my wife´s cup I'm concentrating a lot, concentrate on not making it shake. Once it starts shaking it gets much worse - cannot stop it have to put it down.”

OT: “when I concentrate on my hand shaking it gets worse. If I carry a cup of tea for example if I concentrate on where I'm going it shakes less than when I concentrate on my hand”

OT: “For example carry a tray of tea – I think “I'm going to shake I'm going to shake”. So I ask husband to carry it. When he's not there I carry it not thinking about it and it ends up on the table”

HC: In skateboarding, when trying to make a trick, when I just go with the flow it turns out better than when I try really hard.

HC: “Balancing in yoga – if there are people around it´s better if I don´t concentrate too much otherwise I´m more likely to make a mistake”

OT “Carrying drinks and thinking about not spilling them. If they´re half empty I shake less”

OT: “when in company using knife and fork or lift a glass. Suddenly something I can do quite happily becomes difficult”

FND: “drawing a straight line – the more I try the less straight it is”

FND: “Painting or drawing a straight line, the more I concentrate, the more it goes off. It´s the same with cutting. When I just do it without thinking I’m more accurate”

Interim discussion

Patients seem to agree with the results of the attentional manipulation study results, in that they find their tremor to be worse when they try hard to make their movement perfect. Even some healthy subjects find that trying hard tends to impair their actions.

2.4.3 Improving and worsening factors

These two open questions were included in a written questionnaire (appendix A 1):

What makes your tremor worse? **What makes your tremor better?**

Functional tremor patients

Organic tremor patients

Figure 54: Key words in response to the two questions: What makes your tremor worse? (left) and what makes your tremor better? (right)

Both tremor groups gave fairly similar responses. The answers that clearly differed between the two were the reported worsening with overexertion in the functional tremor group; the worsening when being watched in the organic tremor group; the improvement with distraction in the functional tremor group and their perception that nothing improves their tremor; and finally the improvement with alcohol in the organic action tremor group.

Effect of alcohol

Alcohol, through its disinhibitory effect could be expected to lead to a decrease in the intensity of the attentional focus in functional movement disorders and thus to symptom improvement. Patients were therefore explicitly asked whether alcohol improved their symptoms. Of note, alcohol is known to improve essential and dystonic tremor. Subject who never consume alcohol were excluded. Sixty-nine percent of patients with an organic tremor (18/26) responded that their tremor is improved by the consumptions of alcohol, contrasting to only 13% of patients with a functional tremor (4/30). This difference is significant (Pearson´s chi square $\chi^2(1) = 18.25, p < .001$)

A better way of answering this question would be to test patients tremor before and after the consumption of alcohol. However, because of the detrimental health effects of alcohol, its consumption would never be encouraged by health professionals and thus there is no therapeutic indication in trying to answer this question.

Chapter 3 Agency

3.1 Effect of different attentional foci on sense of agency

As explained in 1.2.2, patients with functional neurological disorders seem to have an abnormal sense of agency over their actions. The following experiment aimed to determine, whether a misdirected focus of attention could lead to a decreased sense of agency. Since functional tremor patients were initially hypothesised to naturally focus on their movement, manipulating their attention onto the movement was expected not make any difference to their sense of agency. However, when their attention is focused on the target, their abnormally low sense of agency should increase towards normal levels.

In controls, both healthy and organic tremor controls, manipulating their attentional focus onto the movement is hypothesised to decrease their sense of agency over their movement. Manipulating their attention onto the target will not have a major effect, since this resembles their natural attentional focus.

3.1.1 Methods

As explained in 1.2.2, intentional binding is an implicit measure of the sense of agency in which the perceived timing of a voluntary action and its effect (typically a tone sounding after a button press) are moved closer together: "bound together" in time.

In order to test the subjects' sense of agency over their reaching movement and the effect different attentional foci have on their sense of agency, an intentional binding task was incorporated into the baseline reaching movement and the reaching movements with implicit attentional manipulation onto the target and onto the movement. Table 63 summarises the number of trials in each condition.

	Number of trials
Pure interval estimate	40
Baseline IB	36-40
Attention to target IB	33-39
Attention to movement IB	33-39

Table 63: Number of trials per condition
IB = intentional binding

3.1.1.1 Pure interval estimate condition

The timing estimate in intentional binding tasks can either be measured using a classic Libet clock or by interval estimation. Using a Libet clock would be too demanding on top of the attentional manipulation task and so the interval estimate method was used.

Estimating sub-second durations is difficult and each subject has their individual bias. The important measure is therefore the difference between the subjects´ interval estimates at baseline, that is without any associated action and the interval estimate with an associated action.

Thus, the baseline timing awareness was established first (Figure 55). A white disk was briefly flashed on a black background and after an interval of 300, 600 or 900ms the tone (400Hz, 70ms duration) sounded. The task was to give a verbal estimate of the duration between the flashing of the white disk and the tone.

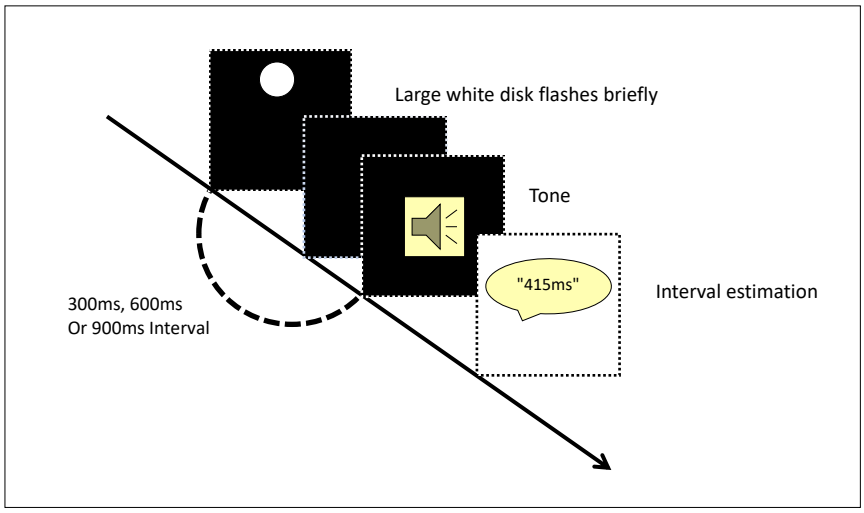


Figure 55: Pure interval estimate

Since the beginning of the interval estimate needed to be very clear cut, the white disk was of a larger size than the usual target (45 pixels instead of 15) and it was only shown for 50ms so as to appear almost instantaneous. Although only three intervals were used, the subjects were told that the interval would vary between 1 and 1000ms. The setup was similar to other interval estimate studies (Moore, Wegner, and Haggard 2009; Wolpe and Rowe 2014). An initial training, aimed at giving subjects a feeling for different interval durations, provided clear examples of different interval durations (200, 600 and 1000ms).

3.1.1.2 Baseline intentional binding condition

The baseline interval estimate condition was incorporated into the reaching movement. Subjects were asked to move their finger from a starting position to the target (box on). As soon as they reached the target, the white disk flashed and after an interval of 300, 600 or 900ms the tone sounded. The task was to estimate the interval between the white disk and the tone.

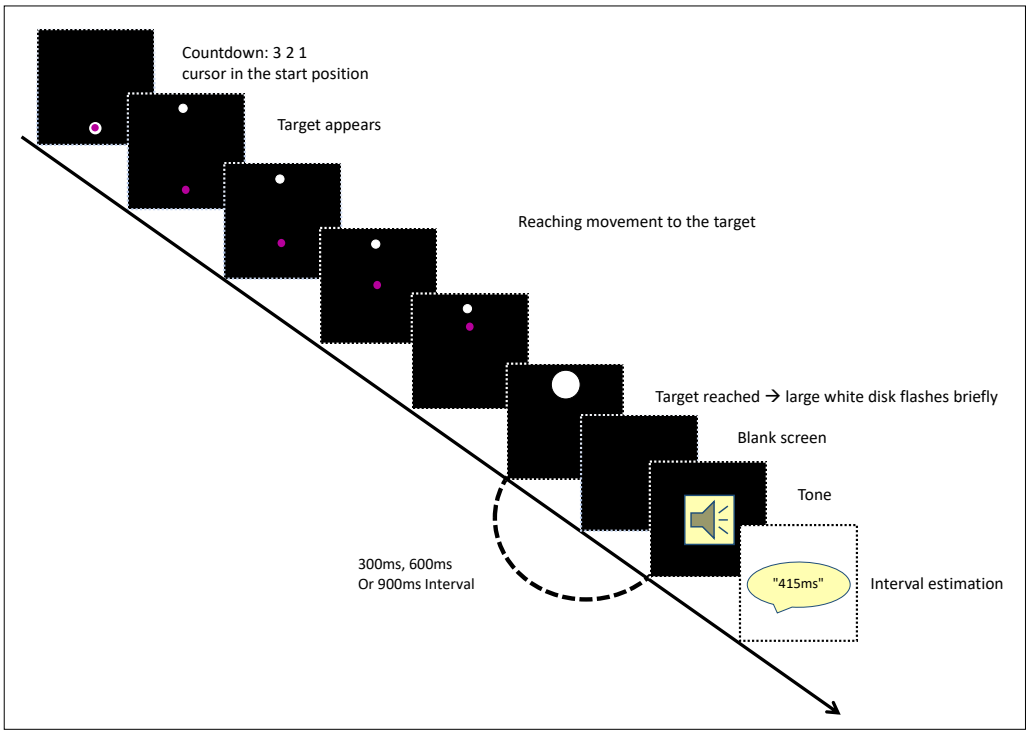


Figure 56: Baseline intentional binding condition

The difference between the true interval and the interval estimate in this condition was compared to the same measure in the pure interval estimate condition. If intentional binding was present, then the perceived duration was to be shorter in this condition than the pure interval estimate condition.

Next the effect of different attentional manipulations (either onto the target, or onto the movement) on intentional binding was evaluated.

3.1.1.3 Attention to target intentional binding condition

Next, it was evaluated, what effect attention to the target had on intentional binding. The condition was the same as the baseline intentional binding condition, but in addition, the target sometimes jumped to either side while the subject was moving towards it. The task was to estimate the interval and say whether or not the target had jumped (Figure 57).

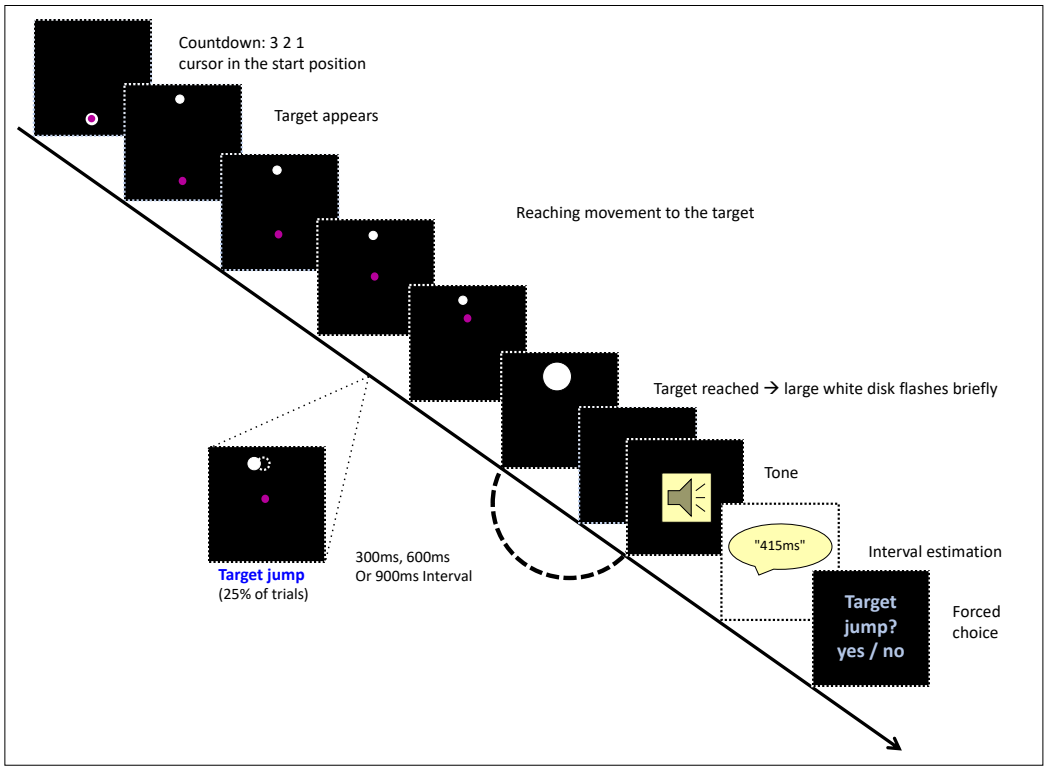


Figure 57: Attention to target intentional binding condition

3.1.1.4 Attention to movement intentional binding condition

Finally, the effect of attention to the movement on intentional binding was evaluated. Again, the condition was the same as the baseline intentional binding condition, but in addition there was sometimes a deviation to either side added to the visual feedback (same as in 2.3.4.1). Once the cursor reached the invisible line the white disc flashed at the location where it crossed the line and after a certain interval a tone sounded. The task was to estimate the interval and say whether or not the visual feedback had been distorted by an added deviation (Figure 58).

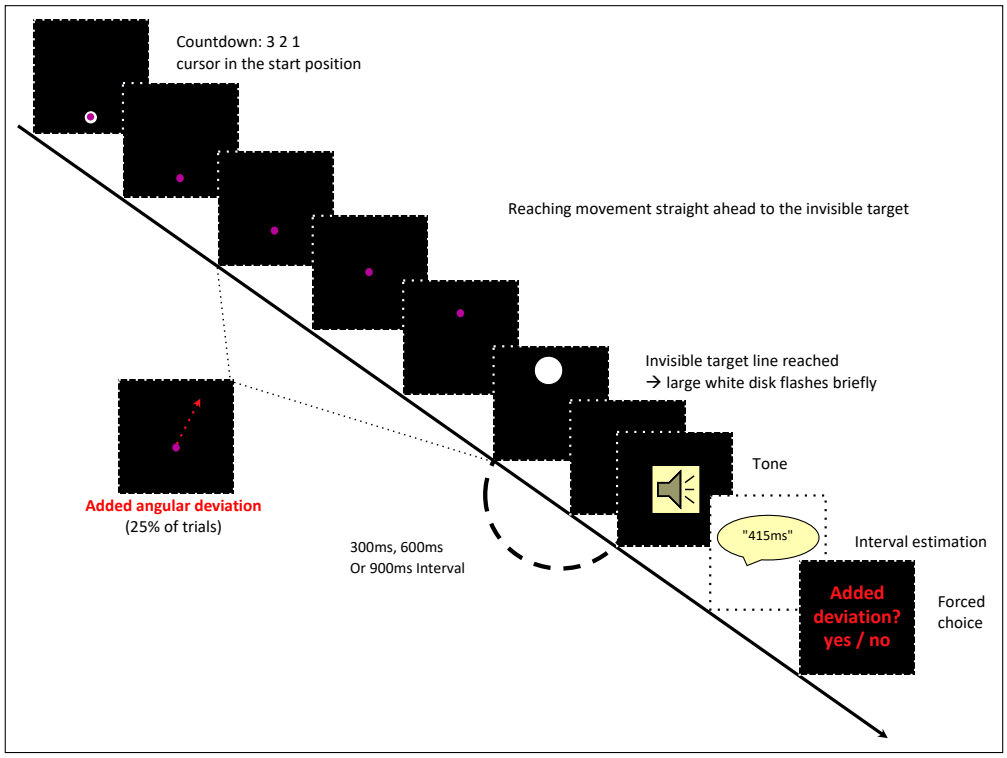


Figure 58: attention to movement intentional binding condition

3.1.2 Results

Before being able to infer any effects of different attentional foci on the sense of agency, I needed to establish if this task induced intentional binding.

In order to answer this question, the pure interval estimate (3.1.1.1) was compared to the interval estimates in which there was an additional movement, i.e. the baseline intentional binding condition (3.1.1.2)). If intentional binding was present, then the interval estimate should be shorter in the intentional binding condition than in the pure interval estimate condition, i.e. baseline movement minus pure estimate should be a negative figure. Looking at the absolute difference of the interval estimates in these two conditions, out of the 18 healthy controls, 12 subjects have a positive difference, only 6 a negative and the overall average is +49.7ms. In the 8 organic tremor patients 5 have a positive difference, 3 a negative one and the overall average difference is +7ms.

Finally, in the 8 functional tremor patients tested, 5 subjects have a positive difference, 3 a negative one and the overall average is -18.2ms. Hence overall, out of 34 subjects, the baseline intentional binding task only seems to induce intentional binding in 12 subjects (see Table 119 in A 7). Thus, the baseline condition does not seem to induce intentional binding.

While this way of analysing the data gives an intuitive answer, a more adequate way of analysing it is by performing a linear regression for each person for both conditions (pure interval estimation and baseline intentional binding condition), with the true interval as the independent variable and the interval estimate as the dependent variable. The slope of the regression line is a good indicator of attention to time. A slope of 0 means that time cannot be perceived at all and a slope of 1 means near perfect time perception (Figure 59).

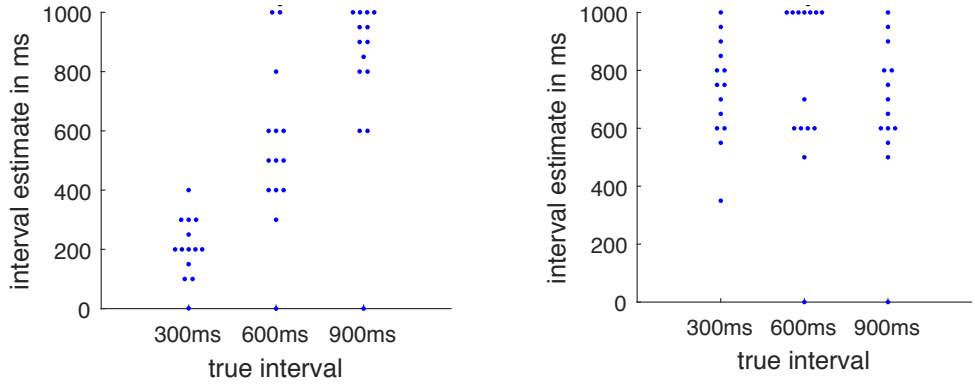


Figure 59: linear regression of true interval over interval estimate
Two different subjects´ interval estimate against the true time interval of the pure interval estimate condition. The figure on the left shows a slope near 1 (1.111) indicating very good attention to time and perception of it. The figure on the right shows a slope near 0 (-0.011) indicating poor attention to time and perception of it.

If the slopes in different conditions are dissimilar, then the intercepts are difficult to interpret. If on the other hand the slopes are similar to each other, then the intercepts are interpretable: if the intercept in the baseline intentional binding condition is lower than the intercept in the pure interval estimate condition, then it indicates intentional binding.

This analysis (detailed in Table 120 in appendix A 7) showed that in healthy controls time perception was good in these two conditions (pure interval estimate: slope 0.88, baseline intentional binding condition: slope 0.79) and their slopes were similar, hence the intercept was interpretable and the intercept increased from -76 to + 28 with the addition of the movement to the task, hence there was no intentional binding.

Similarly, there were no indications of intentional binding in the organic tremor group. Only the functional tremor patients´ average showed a decrease in the perceived interval duration with the

additional movement (intercept 134 decreasing to 50). It is difficult to argue that the task induces intentional binding in the functional tremor group but not in either control group.

Note that the slope, i.e. the attention to time and the perception of it, was almost identical in the FND and OT groups and both were slightly worse than those of the healthy controls in the pure interval estimate condition, but very similar to healthy controls in the baseline intentional binding condition. Hence overall timing perception and attention to it was similar in functional tremor patients compared to controls.

3.1.3 Interim discussion

The baseline condition with movement (just the movement but no attentional manipulation) did not induce any intentional binding in 18 healthy and 8 organic controls.

This means that the task did not induce intentional binding and therefore one cannot deduce any effects of different attentional foci on agency.

It is possible that the appearance of the white disk was perceived as the result of one´s action and not the tone. Remember that in the classic intentional binding task the button press is the action, the tone is the result.

Removing the white disk is unfortunately not an option since the timing of the "action" or in this case the end of it, needs to be very brief and clearly defined.

Taking the entire duration of the movement up to the tone as the duration to be estimated is also not an option since it would lead to subjects counting the seconds during their movement and adapting the speed of their movement.

Interim analysis of these intentional binding conditions thus showed the absence of induced intentional binding in controls and so these conditions were not performed by the subsequent subjects. The only part that was maintained was the baseline intentional binding condition, renamed as the "attentional manipulation beyond the movement" since the interval estimate required one´s attention to be focused on the flash and the tone, i.e. on something occurring right after the movement (2.3.7.1).

3.2 Sense of agency with subliminal versus supraliminal priming

Given that automatic or implicit movements are generally preserved in functional movement disorders, although voluntary or explicit movements are not, one expects subliminal priming to lead to normal reaction times and sense of agency, but supraliminal priming to lead to abnormally slow reaction times and abnormal sense of agency.

Previous subliminal priming experiments have shown that healthy subjects respond faster (Schlaghecken and Eimer 2004) and perceive a higher sense of agency when their response is compatible with the prime (Voss et al. 2017; Wenke, Fleming, and Haggard 2010). The faster reaction time can be attributed to motor preparation being facilitated by the prime. The increased sense of agency has been attributed to the idea of "flow". When everything is compatible, then the action flows easily and one feels in control. When there is an incompatibility along the line, this sense of ease and flow is disturbed, and the resulting sense of agency is decreased. When free to choose, subjects will choose the prime-compatible response more frequently than the prime incompatible one (Schlaghecken and Eimer 2004; Wenke et al. 2010).

Conversely, when the primes are consciously perceived (i.e. presented at supraliminal threshold) the effect is reversed: healthy subjects report a higher sense of agency when they choose the direction opposite to the direction suggested by the prime (Damen, Van Baaren, and Dijksterhuis 2014). It makes sense to feel more in control when deciding to do the opposite of what has been clearly suggested.

The interesting questions in the context of functional movement disorders are the following:

- Is subliminal priming normal in FND?
    - Do they react faster following compatible as opposed to incompatible primes?
    - Do they feel a higher sense of agency with compatible as opposed to incompatible primes?
    - In free choice trials, do they choose prime compatible responses more frequently?
- Is supraliminal priming normal in FND?
    - In fixed choice trials, do they react faster with compatible primes than with incompatible primes?
    - In free choice trials, do they feel a higher sense of agency when they choose the opposite of what has been suggested by the prime?

3.2.1 Methods

3.2.1.1 Participants

Twenty-three patients with a functional neurological disorder (FND), predominantly movement disorders, and 26 age and gender matched healthy controls took part in the experiment. Four patients and seven control subjects were excluded (see 3.2.1.4). Table 64 details the characteristics of the 38 remaining study participants.

	FND (n=19)	**Healthy control** (n=19)
M:F	8:11	9:10
Age: average (range)	46.9y (20-64y)	46.6y (32-79y)
FND type	• Functional tremor: ▪ Upper limb: 14 ▪ Lower limb: 5 ▪ Head: 2 • Functional weakness: 6 • Functional dystonia: 4 • Functional gait disorder: 4 • Functional chronic pain: 2 • Paroxysmal FMD: 5 • NEAD: 3 • Functional stiffness: 2 • Episodic/transient sensory loss: 2 • Foreign accent syndrome: 1 • Concentration difficulties: 1	• none: 19

Table 64: Study participant characteristics
Note that 18 patients had more than 1 type. "Functional gait disorder" means that the gait disorder comprised a functional gait component not explained by any other listed FND type. NEAD=non-epileptic attack disorder.

3.2.1.2 Subliminal and supraliminal priming

The methods were adapted from earlier publications (Vorberg et al. 2003; Voss et al. 2017; Wenke et al. 2010). Participants were seated, at a viewing distance of 65cm, in front of a 19-inch computer screen on which the stimuli were presented. The task was to press a right keyboard key with their right hand as quickly as possible in response to a large target arrow pointing to the right, and a left keyboard key with their left hand in response to a large target arrow pointing to the left (directional arrow "fixed choice"). In the case of a bidirectional target arrow ("free choice"), subjects could chose freely, but still had to make their response as quickly as possible. They were encouraged to choose on the spot and not to follow a fixed pattern.

Before each large target arrow, a small prime arrow pointing either left or right was shown. In the subliminal experiment the prime was presented for only 16.6ms, i.e. subliminally and the subjects were not informed of its presence. In the supraliminal experiment, the prime arrow was shown for 200ms and participants were told to ignore it. The prime arrow and the large target arrow, which also represented the mask were isoluminant. So as to enhance the masking effect, both the prime and the target arrow appeared randomly above or below the fixation point (Vorberg et al. 2003).

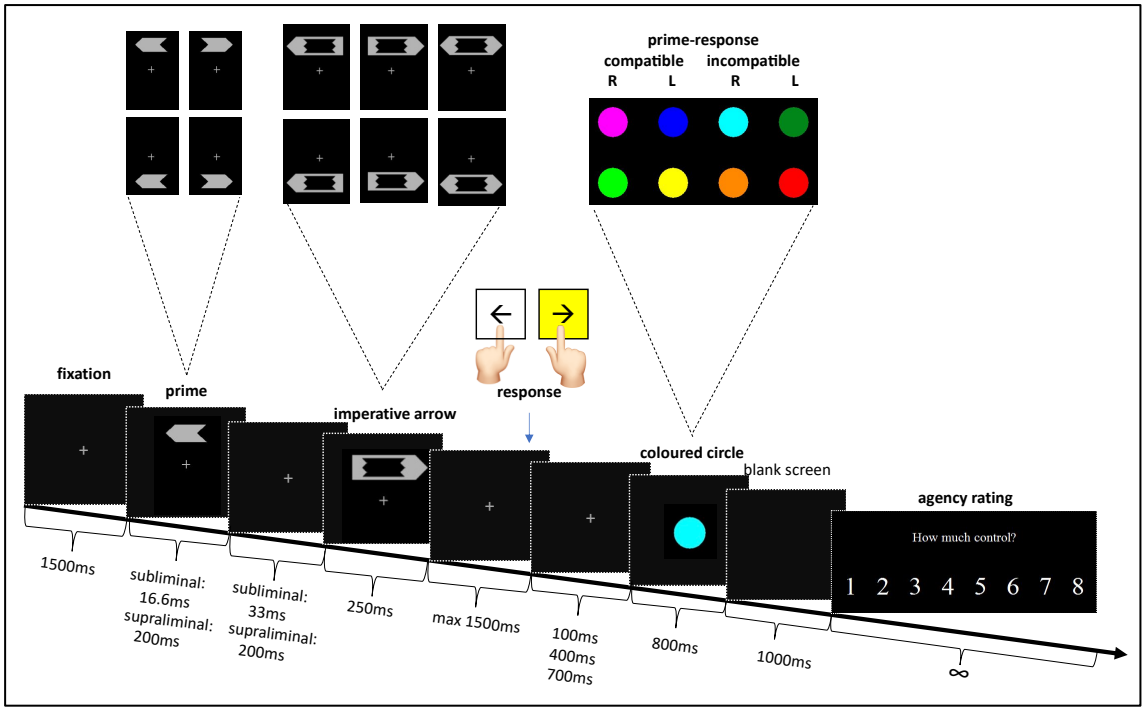


Figure 60: Agency with subliminal or supraliminal priming

If the response was correct and fast enough (maximum 1500ms), a coloured circle appeared on the screen. Unbeknown to the participants, the colour of the circle reflected the congruence of their response to the prime. The eight colours were randomly allocated, so that two colours corresponded to left responses compatible to the prime; two colours corresponded to left responses incompatible to the prime; two colours corresponded to right responses compatible to the prime and the last two to right responses incompatible to the prime.

After each trial, subjects were asked to indicate how much control they felt they had over the coloured circle:

> "We would like you to indicate how much control you felt you had over the appearance of the coloured circle, on a scale from 1 to 8
> 1: no control at all: "I had no control over the colour appearing on the screen"
> 8: complete control: "I had total control over the colour appearing on the screen"

> There are different colours and the delay before the coloured circle appears will also vary. In order to decide how much control you had over its appearance, think about the relationship between what key you pressed and what *colour* you see and *when* it appeared."

The full instructions are available in A 8.1. Note that the interval between subject´s response and the appearance of the coloured circle was 100, 400 or 700ms. This variable interval was introduced so as to give more variability to their sense of agency, since the sense of agency is more marked with shorter intervals.

If the subject´s response was incorrect in case of a directional arrow, or if their response time exceeded 1500ms a large "X" appeared on the screen and the trial in question was repeated up to four times at the end of the experiment. This was performed so as to avoid missing values.

Please refer to the appendix for details of the coloured circles (A 8.2.1), stimuli sizes (A 8.2.2) and presentation durations (A 8.2.3).

All subliminal prime trials were performed separately from all supraliminal prime trials. Which one was performed first alternated between subjects. The subject was informed that the colour attribution changed between the two. The condition performed first contained 12 practice trials, the condition performed second contained two.

The only differences between the subliminal and supraliminal condition, in addition to the display duration of the prime and the interval between the prime and the mask/large arrow, were the total number of trials and the proportion of free choice trials. Since the agency rating in the case of supraliminal primes is most relevant in the free choice condition, a larger proportion of free choice conditions were presented. So as to be able to compare it to the subliminal priming results, fixed choice trials were still included and the cue validity with regards to the target arrow was also 50%.

- Subliminal prime: total 192 trials (6 blocks of 32)
    - 33% prime-fixed response compatible trials (64 trials)
    - 33% prime-fixed response incompatible trials (64 trials)
    - 33% free choice trials (64 trials)
- Supraliminal prime: total 180 trials (6 blocks of 30)
    - 16.6% prime-fixed response compatible trials (30 trials)
    - 16.6% prime-fixed response incompatible trials (30 trials)
    - 66.6% free choice trials (120 trials)

3.2.1.3 Prime visibility test

For the supraliminal condition, a short test at the very start confirmed that the subjects were able to see both the small prime arrow and the larger target arrow.

With regards to the subliminal condition, subjects being able to see the supposedly subliminal prime had to be excluded. A subjective and objective test of prime visibility was performed: Subjects were asked if they had seen anything other than the fixation cross before the large target arrow. They were informed about the presence of the prime and asked to detect the direction of the prime in the subsequent prime visibility test. The settings were identical to those of the subliminal priming study, with the exception of the absence of the coloured circle and agency rating. Furthermore, in order to prevent responding to the large target arrow as in all previous trials, subjects could only respond 600ms after the appearance of the target arrow, when the fixation cross turned green. If the subject reported having sometimes seen the direction of the arrow prime, 120 trials were performed, otherwise 90. After the prime visibility test, subjects were asked again if they had been able to see the direction of the prime arrow.

3.2.1.4 Exclusions

The following subjects were excluded from all analyses:

- Subjects who reported seeing the subliminal prime or whose d' was high (5 HC and 2 FND)
- Subjects who always gave the same agency rating (2 HC and 2 FND)

After these exclusions, 19 subjects remained in each group, which is similar to the numbers reported in the literature (Wenke et al. 2010) included 21 healthy participants, and (Voss et al. 2017) included 16 healthy controls and 16 patients)

The following trials were excluded from all analyses:

- Trials for which the reaction time (RT) remained too slow (>1500ms) or the response incorrect (in the case of unidirectional target arrows) despite up to four repetitions.
- Trials for which the reaction times fell more than 1.5 times the interquartile range above the 3rd quartile or below the 1st quartile of that specific condition (i.e. forced choice, or free choice) within each subject (Table 65).

	subliminal		supraliminal	
	Forced choice	Free choice	Forced choice	Free choice
HC	5.5%	4.0%	3.4%	3.8%
FND	5.0%	4.4%	5.2%	3.0%

Table 65: Percentage of trials excluded as outliers
These trials were excluded as outliers, because their reaction times were 1.5x the interquartile range above the 3rd quartile or below the 1st quartile of that specific condition for that subject.

3.2.2 Results

3.2.2.1 Subliminal priming

The interesting questions are whether subliminal priming is normal in FND. Do FND patients have faster reaction times and perceive a higher sense of agency with compatible compared to incompatible primes? When they have a choice, do they choose prime compatible responses more frequently than prime incompatible responses?

For both the reaction time and the sense of agency, the data was analysed by means of a mixed model ANOVA with group as the between-subject factor and prime-response congruence as the within-subject factor. Given the repeated measures design, the assumption of sphericity was checked in each case but did not require any adjustment using Greenhouse-Geisser's ε.

Reaction time

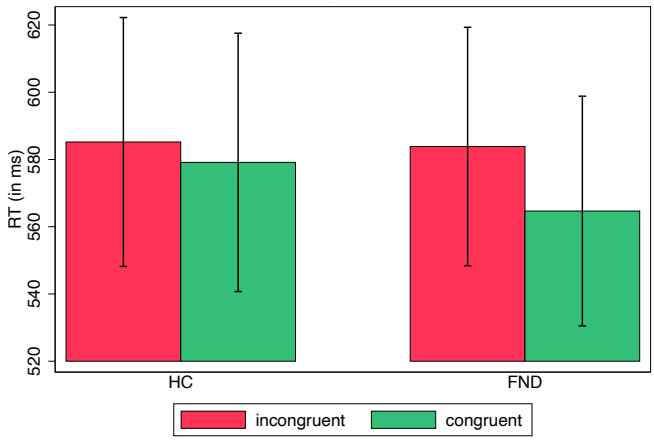


Figure 61: Subliminal priming RT (raw data)
Average reaction times per group for prime-response incongruent versus congruent responses, irrespective of the type of choice (unidirectional or bidirectional target arrow). The standard error of the mean is shown by the error bars.

Assumptions check

The reaction times of the congruent and incongruent trials in the healthy controls and the reaction times of the incongruent trials in the FND group were not normally distributed (Shapiro Wilk *p*

= .00515, p = .00197 and p = .0205 respectively). Those of the congruent trials in the FND group could be assumed to have a normal distribution (Shapiro-Wilk p = .06663). However, Levene´s equality of variance test indicated, that the congruent and the incongruent condition could be assumed to have equal variances between the two groups (p = .87 and p = .77 respectively). Since ANOVA is fairly robust to departures from normality as long as the sample sizes and variances between groups are equal, mixed model ANOVA was be performed on the raw data.

Mixed model ANOVA

A mixed model ANOVA with group as between-subject factor and congruence as within-subject factor, with fixed and free choices collapsed together, gave a significant main effect of congruence ($F(1,36) = 15.10$, $\eta_p^2 = .30$, $p = .0004$) and a trend in the group x congruence interaction ($F(1,36) = 4.08$, $\eta_p^2 = .10$, $p = .0509$). The main effect of group was not significant ($F(1,36) = 0.02$, $\eta_p^2 = .0007$, $p = .88$). Inspection of (Figure 61) showed that reaction times are significantly faster with compatible compared to incompatible primes and there was a trend for this to be even more pronounced in the FND group.

Faster reaction times with compatible subliminal primes as opposed to incompatible subliminal primes were also the case for each choice condition separately (Figure 62).

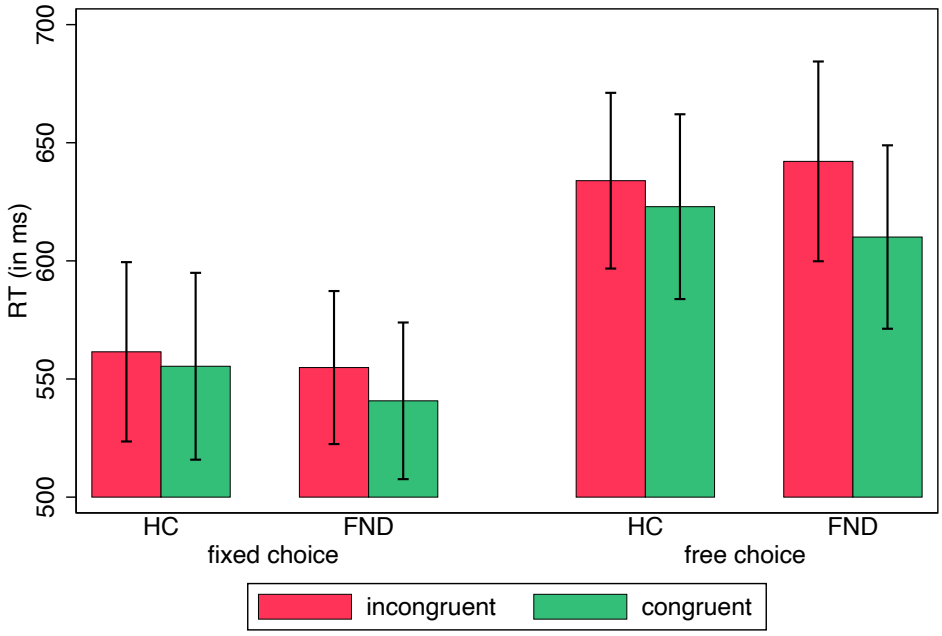


Figure 62: Subliminal priming RT for fixed and free choices (raw data)
The average reaction times per group for prime-response congruent versus incongruent responses are plotted separately for fixed and for free choices. The standard error of the mean is shown by the error bars.

Agency

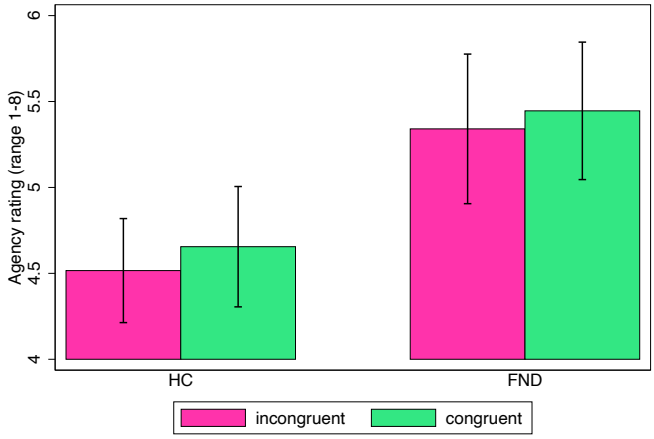


Figure 63: Subliminal priming agency ratings (raw data)
Average agency ratings per group for prime-response incongruent versus congruent responses, irrespective of the type of choice (unidirectional or bidirectional target arrow). The rating ranges from 1 (absolutely no control) to 8 (complete control). The standard error of the mean is shown by the error bars.

Assumptions check

For the mixed ANOVA with group as between factor and congruence as within-subject factor, all combinations of these two factors were normally distributed (Shapiro-Wilk for prime-congruent responses in HC p = .700, in FND p = .153, and for prime-incongruent responses HC: 0.98, FND 0.089). Levene´s test for homogeneity of variance across the groups was insignificant for both the incongruent (p = .15) and the congruent (p = .65) responses. The raw data thus met the assumptions of the mixed model ANOVA.

Mixed model ANOVA

A mixed model ANOVA with group as between-subject factor and congruence as within-subject factor, with fixed and free choices collapsed together, did not give a significant main effect of congruence ($F(1,36) = 0.87$, $\eta_p^2 = .024$, $p = .36$) nor of the interaction group x congruence ($F(1,36) = 0.02$, $\eta_p^2 = .0005$, $p = .90$). Thus, the slight differences between the congruent and incongruent agency ratings seen in Figure 63 were not significant, nor was there a difference in the agency rating to prime congruent versus incongruent responses between the groups. The main effect of group was of no interest for the agency ratings, since it simply represented the subject´s tendency to use higher or lower values on the rating scale.

There is an argument to be made for perceiving a higher sense of agency with prime compatible as opposed to incompatible choices regardless of whether there is free choice or not. However, one could argue that the agency rating is most relevant in the case of free choices (bidirectional target arrows). The analysis was thus repeated, taking only free choice responses into account. The results of the mixed model ANOVA were, however, not significant for the main effect of

congruence nor for the interaction group x congruence. Details of the assumptions check and mixed model ANOVA are in A 8.3.1. Figure 64 shows the results for fixed and free choices separately.

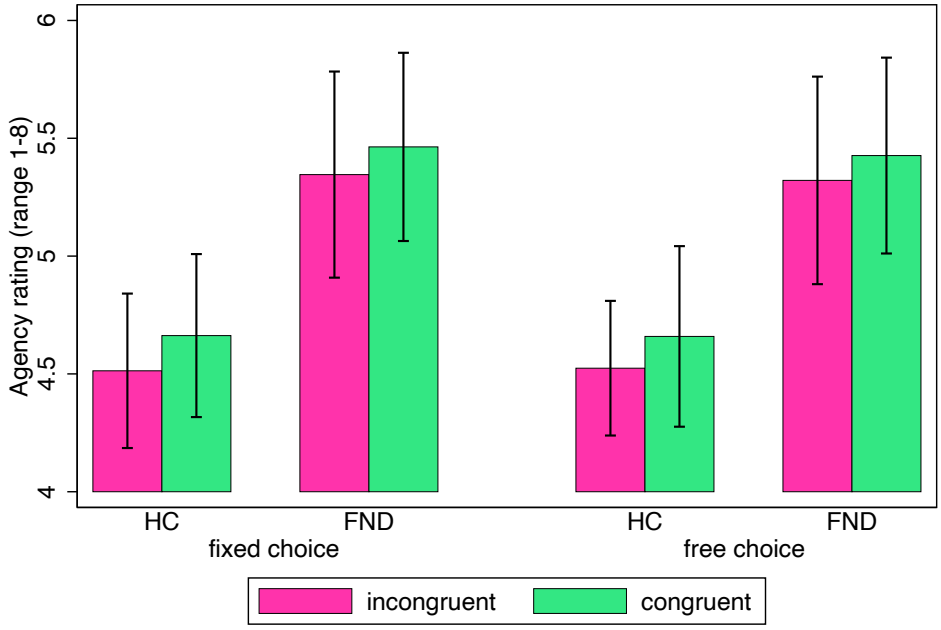


Figure 64: Subliminal priming agency ratings (raw data)
Average ratings per group for prime-response congruent versus incongruent responses, separately for the two choice types (fixed choice with unidirectional target arrows and free choice with bidirectional target arrows). The rating ranges from 1 (absolutely no control) to 8 (complete control). The standard error of the mean is shown by the error bars.

Chosen direction in free choice conditions

The question is whether in the free choice condition, in which healthy controls tend to choose more prime-congruent than incongruent responses, patients with FND show the same pattern or not.

	Congruent	Incongruent
HC (n=19)	53.1%	46.9%
FND (n=19)	54.4%	45.6%
Mann-Whitney rank sum test	Z = -0.70, r=-.16	
	p = .48	

Table 66: Subliminal prime congruent and incongruent responses in free choice trials

Since the percentage of congruent choices were normally distributed for the healthy controls (Shapiro-Wilk p = .65), but not for the FND group (Shapiro-Wilk p = .044), a two-sample Wilcoxon rank-sum (Mann-Whitney) test was performed, which did not reveal any significant difference between the two groups (Table 66).

Taking both groups together, Wilcoxon signed rank test with a hypothesised mean of 50 refuted the hypothesis that the responses were the same as chance (Z =2.78, r = .45, p = .0055). Thus, subjects chose significantly more congruent than incongruent responses in free choice trials.

However, when analysing each group separately, this could only be upheld for the FND group (A one sample t-test with a hypothesised mean of 50 for the healthy controls was not significant (t(18) = 1.66, Cohen´s d = 0.38, p = .11). For the FND group the non-parametric Wilcoxon signed-rank test was just significant (Z = 1.97, r =.45, p = .0486).

3.2.2.2 Supraliminal priming

Healthy controls have previously been found to have a higher sense of control in free choice trials when they choose the opposite of what has been suggested by the supraliminal prime (Damen et al. 2014). The question is whether the same or a different pattern is present in FND patients.

The other relevant question is whether compatible supraliminal primes lead to faster reaction times as opposed to incompatible supraliminal primes in fixed choice trials. Note, however, that the prime – target arrow congruence was 50%, thus it was in fact not predictive.

Reaction time

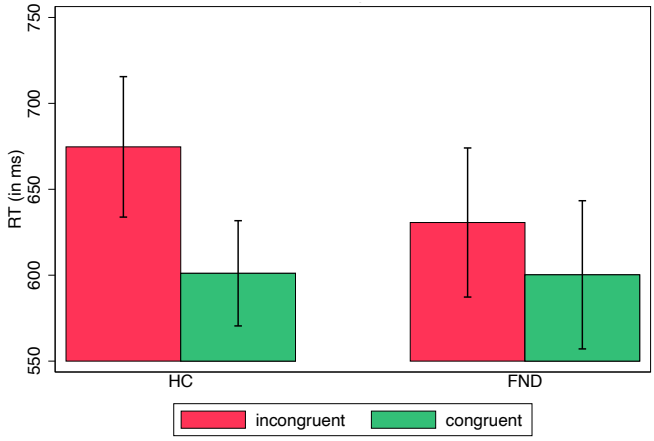


Figure 65: RT in supraliminal fixed choice trials (raw data)
Average reaction times per group for prime-response congruent versus incongruent responses, for fixed choice trials only (unidirectional target arrows). The standard error of the mean is shown by the error bars.

Assumptions check

All these include fixed choice responses only. The Shapiro-Wilk test was only significant for the incongruent responses in the FND group (p = .033). For all other combinations of the group and congruence factors, the Shapiro-Wilk test did not reject a normal distribution (Shapiro-Wilk for prime-congruent responses in HC p = .53, FND p = .089, and for prime-incongruent responses in HC p = .56). Levene´s test for homogeneity of variance across the groups was insignificant for both the incongruent (p = .99) and the congruent (p = .31) responses. Although there was a mild violation of the assumption of normality, ANOVA was robust to this, since the sample size and variances were similar. The raw data was thus analysed. Given the repeated measures design, the assumption of sphericity was checked but did not require any adjustment using Greenhouse-Geisser's ε.

Mixed model ANOVA

A mixed model ANOVA of the reaction times with group as between-subject factor and congruence as within-subject factor, for the fixed choices, gave a significant main effect of congruence ($F(1,36) = 9.94$, $\eta_p^2 = .22$, $p = .0033$) but not of group ($F(1,36) = 0.17$, $\eta_p^2 = .005$, $p = .68$), nor of the interaction group x congruence ($F(1,36) = 1.71$, $\eta_p^2 = .045$, $p = .20$).

Agency

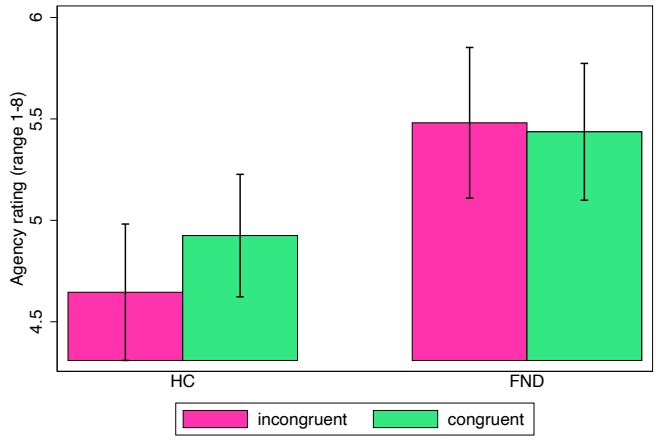


Figure 66: Agency rating in supraliminal free choices (raw data)
Average agency ratings per group for prime-response congruent versus incongruent responses, for free choice trials only (bidirectional target arrows). The rating ranges from 1 (absolutely no control) to 8 (complete control). The standard error of the mean is shown by the error bars.

Assumptions check

All these included free choice responses only. The Shapiro-Wilk test did not reject the hypothesis of a normal distribution for all combinations of the group and congruence factors (Shapiro-Wilk for prime-congruent responses in HC $p = .15$, in FND $p = .97$, and for prime-incongruent responses HC: 0.78, FND: $p = .64$). Levene´s test for homogeneity of variance across the groups was insignificant for both the incongruent ($p = .68$) and the congruent ($p = .80$) responses. The assumptions of the mixed model ANOVA were met by the raw data, thus no normalisation was required. Given the repeated measures design, the assumption of sphericity was checked but did not require any adjustment using Greenhouse-Geisser's ε.

Mixed model ANOVA

A mixed model ANOVA of the agency ratings in free choice trials, with group as between-subject factor and congruence as within-subject factor did not give a significant main effect of congruence ($F(1,36) = 0.68$, $\eta_p^2 = .019$, $p = .41$) nor of the interaction group x congruence ($F(1,36) = 1.30$, $\eta_p^2 = .035$, $p = .26$).

Chosen direction in free choice conditions

It was not an interesting research question as to whether subjects chose more or less prime-congruent responses in the supraliminal free choice trials. The data was simply shown so as to exclude any systematic bias.

	Congruent	Incongruent
HC	55.7%	44.3%
FND	56.9%	43.1%
Mann-Whitney rank sum test	Z = -0.75, r = -.17	
	p = .46	

Table 67: Supraliminal prime congruent and incongruent responses in free choice trials

Since the percentage of congruent choices were normally distributed for the healthy controls (Shapiro-Wilk p = .079), but not for the FND group (Shapiro-Wilk p = .028), a two-sample Wilcoxon rank sum (Mann-Whitney) test was performed, which did not reveal any significant difference between the two groups (Table 67). Wilcoxon signed rank test with a hypothesised mean of 50 for both groups taken together or for the FND group alone did not conclude that the responses were any different from chance level (both groups together: Z = 1.62, r = .26, p = .10; FND only Z = 1.65, r = .38, p = .099). A one sample t-test with a hypothesised mean of 50 for the healthy controls was not significant either (t(18) = 1.30, Cohen´s d = 0.30, p = .21).

3.2.2.3 Subliminal versus supraliminal priming

Taking only free choice trials into account, was there a difference in agency rating between the two groups according to whether the prime was presented subliminally or supraliminally? In other words, did FND patients have normal agency rating in the subliminal, but not in the supraliminal free choice condition?

The assumptions for normality and equality of variance have already been checked above and were met. A mixed model ANOVA with group as between-subject factor and prime type (subliminal versus supraliminal) and congruence as within-subject factor, did not show a main effect of prime ((F(1,36) = 1.02, η_p^2 = .027, p = .32) or congruence(F(1,36) = 1.16, η_p^2 = .031, p = .29), nor an interaction effect of group x prime (F(1,36) = 0.16, η_p^2 = .0043, p = .70), nor group x congruence (F(1,36) = 0.64, η_p^2 = .018, p = .43), nor group x prime x congruence (F(1,36) = 0.56, η_p^2 = .015, p = .46).

3.2.3 Interim discussion

The aim of this experiment was to establish, whether subliminal priming is normal in functional movement disorders. This was hypothesised to be the case, in view of the generally preserved implicit or automatic movements. Conversely, supraliminal priming was hypothesised to be abnormal since voluntary movements are typically impaired and associated with a lack of perceived agency.

The findings show that ***subliminal*** priming is normal in functional neurological disorder, in so far as reaction times and free choices are concerned: reaction times are faster with prime congruent responses and in free choice trials more prime compatible responses are chosen. There is even a trend for both these effects to be stronger in the FND group: there is a trend for their reaction times to congruent as opposed to incongruent primes to be faster than in the healthy controls and there is a trend for FND patients to choose more prime congruent responses in free choice trials than healthy controls. To the best of my knowledge, this is the first subliminal priming study in functional neurological disorders, and as predicted, subliminal priming for motor responses is normal in FND.

With regards to the sense of agency in subliminal priming and hence the subjective experience, this study did not find any significant difference between the patients and healthy controls, but it also failed to replicate a previous study in which healthy controls felt more control with prime-response congruent as opposed to prime-response incongruent choices. Although the effect pointed in this direction it did not reach statistical significance. Measuring the sense of agency is inherently difficult, and in this case, it was not sensitive enough to highlight any possible differences. Thus, it cannot be said with certainty, if the sense of agency is being modulated differently, but based on the findings of the current study only, one can argue that there is no significant difference in the sense of agency with subliminal priming between functional neurological patients and healthy controls.

With regards to fixed choices in ***supraliminal*** priming with non-predictive cue validity (i.e. prime validity of 50%), both patients and healthy controls respond faster with compatible than with incompatible primes, but there is no difference between the two groups. There is also no significant overall difference in reaction times between groups.

In contrast, a previous study, using abstract symbols to indicate left or right responses, failed to show any difference in RT in either healthy controls or FND patients in response to valid as opposed to invalid supraliminal primes in conditions in which the prime validity was 50% (Pareés et al. 2013).

The agency rating with supraliminal primes in free choice trials was not affected by whether or not the response was congruent to the prime or not and there was again no difference between the groups.

Finally, despite my initial hypothesis, there was no difference in the agency rating in free choice trials between the two groups with subliminal versus supraliminal primes.

One can therefore conclude that subliminal and supraliminal priming with non-predictive cues in functional neurological patients is not dissimilar to that of healthy controls with regards to reaction times and sense of agency.

Two previous supraliminal priming studies showed faster reaction times with high cue predictability (95% valid as opposed to non-predictive (50%)) in healthy controls, but slower or unchanged reaction times with high cue predictability in FND (Pareés et al. 2013; Teodoro, Meppelink, et al. 2018). Similarly, when a joystick movement could be prepared (because the location it needed to be moved to as quickly as possible once the go cue appeared was known in advance), functional movement disorder patients' movement times became gradually slower across the block (Pareés et al. 2013). Thus, other studies have shown that patients with FND differ from healthy controls, with regards to reaction times or speed of movement not in 50% prime validity conditions, but when the supraliminal primes are highly predictable. The same might apply to the sense of agency. A separate condition with a higher cue predictability (95% predictive) could therefore be introduced and its effect on the sense of agency analysed. In addition, a neutral prime could be incorporated, so as to allow to differentiate between improved responses with valid or more impaired responses with invalid primes.

Chapter 4 Beliefs

4.1 Perception of tremor severity

Given the apparent pivotal role of beliefs in the pathophysiology of functional neurological disorders, the question arises as to whether the beliefs about their symptoms are abnormal in FND patients. Their perception of their tremor severity in the attentional tasks mentioned above was therefore tested both in retrospect and in real-time.

4.1.1 Methods

4.1.1.1 Retrospective

A Matlab® script analysed the total pathlength and the maximum deviation away from a perfectly straight line for the trajectories drawn by the subject on the touchpad. The trajectory corresponding most closely to the average was chosen and distorted into straighter and shakier versions.

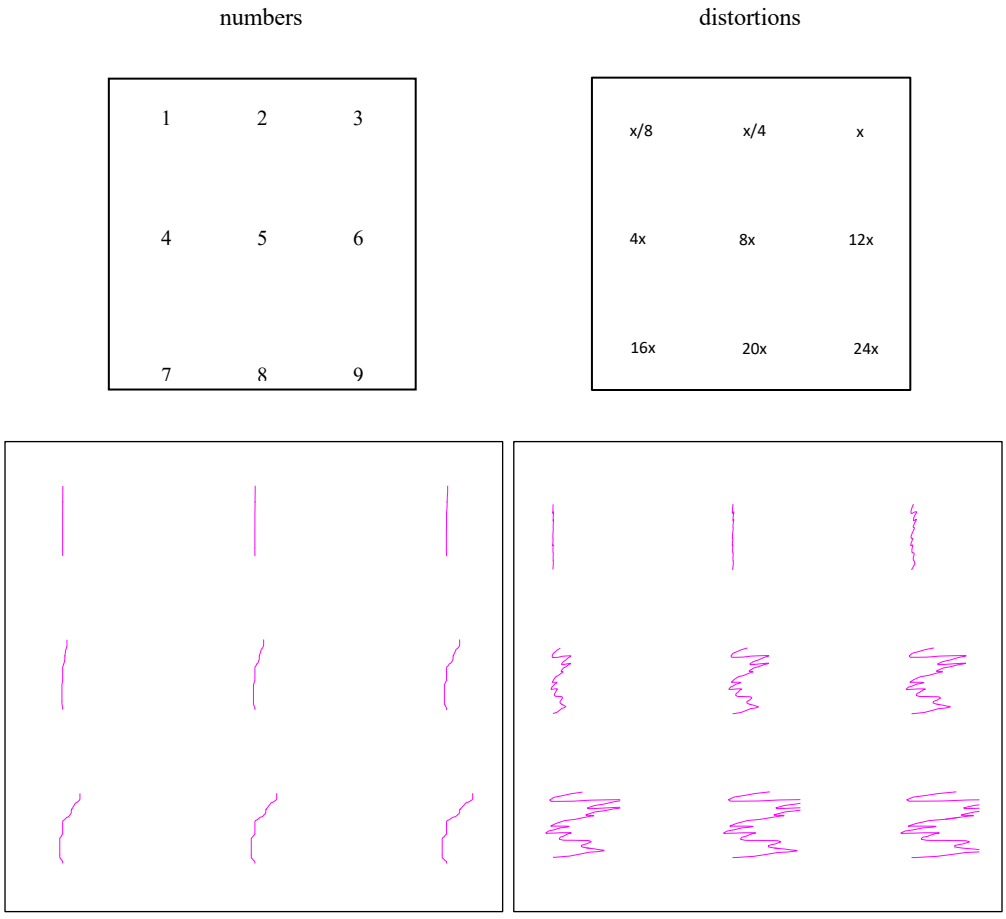


Figure 67: Numbers to choose from, applied distortions and examples of two subjects' average trajectory with the applied distortions
Number 3, in the top right corner was the subject´s unmodified typical trajectory (x remains unchanged). Numbers 1 and 2 (the first 2 trajectories) are the same trajectory straightened out and numbers 4-9 (2nd and 3rd rows) are the same trajectory made progressively shakier. Lower panel: left: healthy control example, right: functional tremor example.

In order to straighten out the trajectory or make it shakier, each x value was modified as indicated in Figure 67 for the corresponding positions of the resulting nine trajectories: to make it straighter every x coordinate was divided by 4 or 8, to make it shakier, each x coordinate was multiplied by 4, 8, 12 etc. The resulting nine trajectories were shown to the subjects, who needed to decide which one of them was their typical trajectory.

This was done for both the trajectories with and without the box. Without the box all trajectories excluding the repetition of the baseline box off trajectories were included (since the repetition was not performed in every participant).

For the box on conditions all the trajectories without any perturbation, i.e. without added deviation or target jump, and also the trajectories to the start for the following conditions were included: baseline trials, deviation/no deviation and target jump/no jump conditions.

4.1.1.2 Online

While the subject moved towards the target, the feedback they saw (the purple coloured cursor dot) moved either exactly as their finger did, or it moved in a shakier or less shaky manner (Figure 68 and Table 68). After each trial, the subject could tweak the shakiness of the feedback until they felt that the purple cursor moved exactly as they did. In other words, their task was to tweak the shakiness of the feedback until they perceived it as being a true reflection of their movement.

The initial shakiness varied randomly between each of the 11 possibilities (5 gradually straighter feedbacks, unperturbed feedback, 5 gradually shakier feedbacks) and the whole condition was performed 11 times so as to start with each distortion once (Table 68).

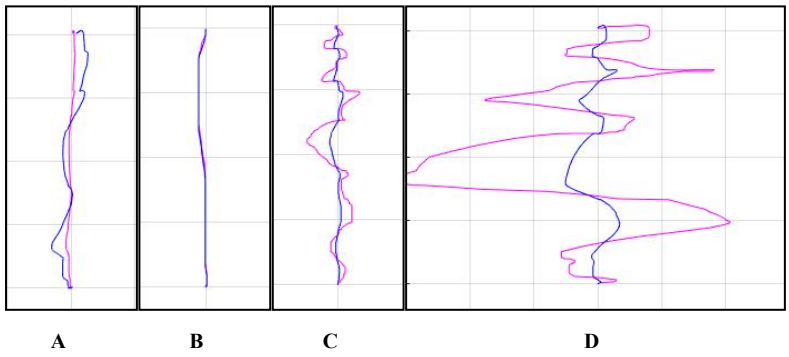


Figure 68: Distorted online feedback
The purple line shows the trajectory of the purple coloured cursor shown as feedback. The actual trajectory drawn by the subject is shown in blue (not shown to the subject). A: visual feedback is smoother than it is in reality. B: the visual feedback matches the subject´s finger movement exactly. The visual feedback is a bit (C) and a lot (D) shakier than it is in reality. Note that this condition was performed with the box and that the subject only saw the movement of the purple coloured dot, not its resulting line.

The distortion factors were the following:

Chosen value	1	2	3	4	5	6	7	8	9	10	11
Corresponding distortion factor	x/10	x/8	x/6	x/4	x/2	x no distortion	2x	4x	6x	8x	10x

Table 68: Distortion factors according to the chosen value
The distortion factors varied from x/10 (i.e. straightening out the visual feedback by dividing each x coordinate by 10), to 10x (i.e. making the shown trajectory much shakier by multiplying each x coordinate by 10). Note that a chosen value of 6 meant that there was no perturbation of the trajectory, that it was a true representation of the finger movement.

4.1.2 Results

4.1.2.1 Retrospective

There was no difference between the groups in their retrospective perception of their tremor severity compared to their actual tremor severity, neither in the box on condition, nor in the box off condition. The "equivalent distortion factor" in Table 69 is the number by which each x coordinate was multiplied (see 4.1.1.1).

Although all the group averages of the chosen trajectory were superior to 3, (3 being no distortion or the subject´s typical trajectory), one sample t-test asking whether or not the chosen number was significantly different from a chosen number of 3, showed that only the healthy controls were significantly different (both box on ($t(19) = 3.9$ $p = .0009$) and box off ($t(19) = 4.16$, $p = .0005$)).

	With indirect visual feedback (box on)		**With direct visual feedback (box off)**	
	Chosen trajectory number from 1 to 9 according to Figure 67 (group average)	**Equivalent distortion factor** factor by which each x coordinate is multiplied (group average)	**Chosen trajectory** number from 1 to 9 according to Figure 67 (group average)	**Equivalent distortion factor** factor by which each x coordinate is multiplied (group average)
HC (n=20)	3.6	2.8	3.9	3.7
OT (n=19)	3.9	3.7	4.37	5.5
FND (n=20)	3.65	2.95	4	4
One-way ANOVA	$F(2,56) = 0.69$		$F(2,56) = 1.10$	
	$p = .51$		$p = .34$	

Table 69: Retrospective tremor perception results
Remember that a chosen trajectory of 3 means no distortion

4.1.2.2 Online

There was a trend for there being a significant difference in the chosen distortion number between the three groups (Table 70). A one-sampled t-test on the chosen distortion numbers in healthy controls rejected the null hypothesis that this sample came from a distribution with a mean of 6 (6 meaning no distortion) ($t(19)= -4.77$, $p = .0001$). For the organic group this null hypothesis could not be rejected (OT $t(17)= -0.48$, $p = .63$).

	Chosen distortion (from 1 to 11) (group average)	**Equivalent distortion factor** (group average)
HC (n=20)	5.4	0.7
OT (n=18)	5.5	0.8
FND (n=19)	6	1.0
One-way ANOVA	$F(2,54)=2.95$	
	$p = .061$	

Table 70: Online tremor perception results
Remember that a chosen distortion of 6 is the unperturbed feedback

4.1.3 Interim discussion

One could interpret the data as indicating that functional and organic tremor patients are good at estimating their tremor, be it online or retrospectively, and healthy controls underestimate their deviations away from a perfectly straight line when evaluating their shakiness online and overestimate their shakiness retrospectively. However, since the healthy controls have almost perfectly straight lines, the slight effects of the manipulations make hardly any difference at that level of distortion or straightening, hence it is easy to pick one rather than the other (see the upper row of the left lower panel in Figure 67).

Thus, a more adequate interpretation is that the three groups estimate the shakiness of their movements well, be it retrospectively or online.

In a previous study tremor patients perceived their tremor as being present for longer durations throughout the day than it was in reality, and functional tremor patients did so to a much larger extent than organic tremor patients (Pareés et al. 2012). Since that study regards durations, rather than severity, the findings are not too surprising. As already mentioned, functional symptoms are typically present, when patients pay attention to them and improve or even disappear with distraction. Thus, every time the patients check if their tremor is present or not, their attention brings it out and when the tremor is absent, their attentional focus is elsewhere and they are thus not aware of its absence. It is not surprising that they therefore conclude that the tremor is present throughout most of the day. In addition, the times when the tremor is a hindrance will carry more weight when recording the duration of the tremor at the end of the day, than the times when the movements were performed smoothly due to the absence of tremor, since those times will pass unnoticed. This might explain overreporting even in organic tremor patients.

How do my findings fit in with another study, in which patients with functional motor symptoms subjectively rated their symptoms worse, than when they were asked to evaluate a simultaneously taken video recording ((Ricciardi et al. 2015))? In comparison to a healthcare professional there was a trend for the rating being worse in the patients with FND. The fact that patients showed a trend for a worse rating compared to the healthcare professional is not surprising, since healthcare professionals are used to seeing severely affected patients. Patients on the other hand, generally compare themselves to their premorbid state. In addition, an abnormality, affecting oneself may naturally be perceived as more severe, because of the subjective experience of the impairment. There remains thus the difference in the subjective rating from memory, compared to the rating when evaluating the video. One might conclude, that when presented with objective evidence (the video recording in the published study or the trajectories in the present study), functional movement disorder patients do not overrate their symptoms.

4.2 Changing beliefs by modifying feedback

If beliefs play an important role in the pathophysiology of functional neurological disorders, an important therapeutic question is whether these beliefs can be changed and lead to symptom improvement. Specifically, given functional tremor patients' attentional focus seems to lie on the visual feedback of their movement (see 2.2), does changing the visual feedback lead to changes in beliefs and thereby to symptom improvement in functional tremor?

4.2.1 Short duration feedback modification

4.2.1.1 Methods

The distorted online feedback condition described in 4.1 allows the analysis of whether or not a distorted feedback can improve or worsen tremor.

4.2.1.2 Results

As can be seen in Figure 69, the two control groups behave similarly: making the visual feedback smoother, less shaky, has no effect on the resultant path length of that trial; making it more and more shaky, increases the resultant path length. No clear pattern can be seen in the FND group, except for a possible worsening with increased shakiness of the feedback.

Looking at each FND subject individually (Figure 70), reveals the same pattern: making the visual feedback smoother has no effect on path length for most FND patients, making it more and more shaky leads to a worsening of the path length in the majority.

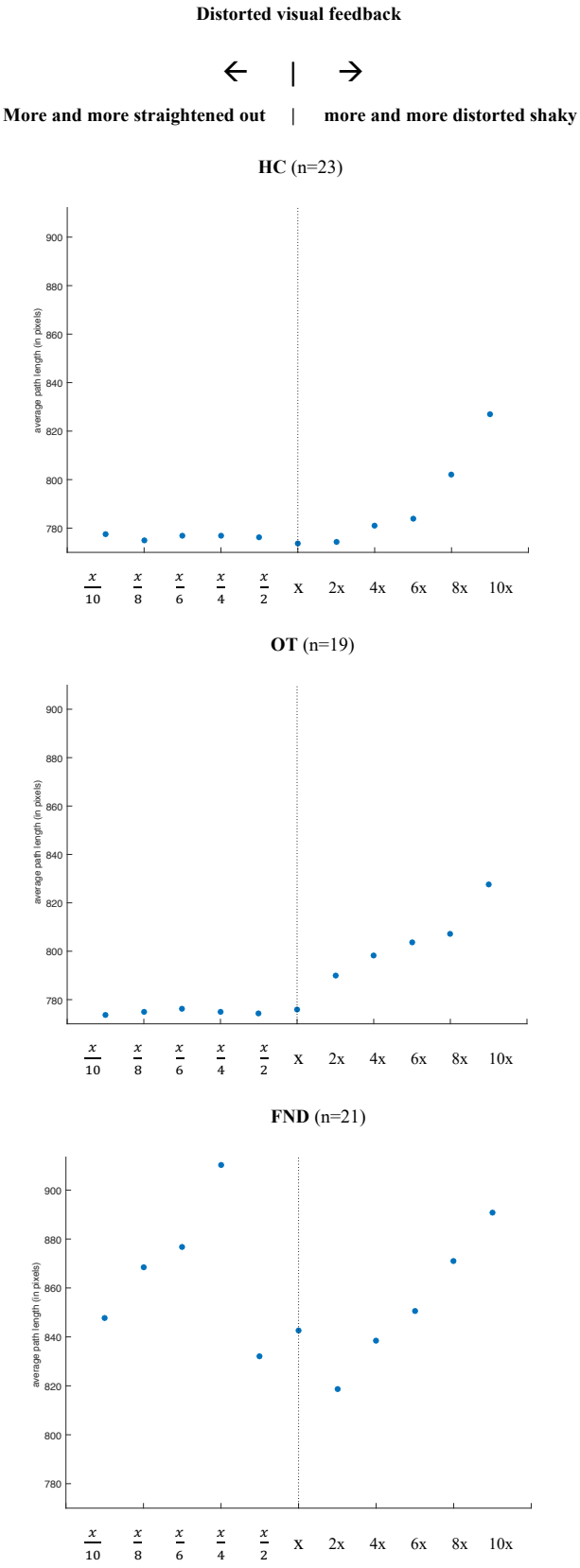


Figure 69: Distorted visual feedback and resultant path lengths (group averages)
The X axis shows the distortion factors going from x/10 (i.e. straightening out the trajectory by dividing each x coordinate by 10), over 1x (meaning no distortion), to 10x (i.e. making the shown trajectory shakier by multiplying each x coordinate by 10). A dotted line is drawn through the point at which there is no distortion. All the points to the left of this line correspond to smoothened out visual feedbacks, all the points to the right, to more and more shaky feedbacks.

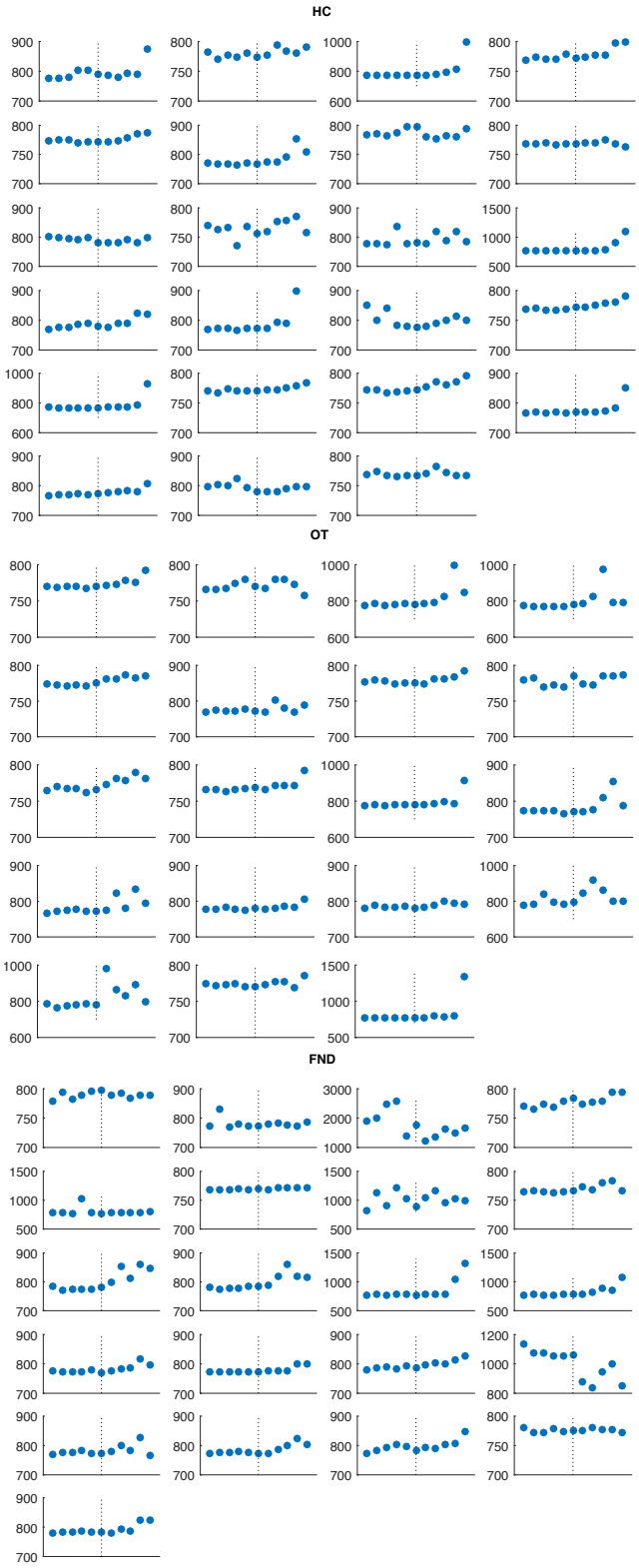


Figure 70: Distorted visual feedback and resultant path lengths for each individual subject
Note that the Y axis, indicating the path length in pixels varies between different subjects. The X axes are identical to the X axis in Figure 69. A dotted line is drawn through the point at which there is no distortion. The points to the left of this line correspond gradually more smoothened out visual feedbacks, all the points to the right, to gradually shakier feedbacks.

4.2.1.3 Interim discussion

The lengthening of the path length with increasingly more distorted/ more shaky feedbacks is likely attributable to overcorrection: with the most extreme distortion, an actual movement of one pixel to the side leads to a feedback of a movement of ten pixels to the side and so the correction that is applied is larger than one pixel, which again leads to an exaggerated visual feedback. All three groups show this effect. Smoothing out the visual feedback has no clear effect on either group.

Thus, a smoothing out of the visual feedback does not change the tremor on the ongoing trial. Could it be that the distorted visual feedback needs to be applied over a prolonged period to lead to any effect? This possibility is evaluated in the next experiment.

4.2.2 Intermediate duration feedback modification

4.2.2.1 Methods

The settings were the same as for the attentional manipulation conditions with subjects moving their finger on a touchpad, which was hidden by a box with a horizontal screen on which the starting point, the target and their current finger position were displayed. The task was to move the cursor into the target. After subjects had performed many reaching movements described in 2.2 and 2.3, they were asked to perform another 10 baseline trials ("baseline pre" condition). Following these they were told that the computer program had analysed all their previous trajectories, and found their average trajectory, i.e. their average shakiness. They were told that from now on, if they were shakier than their average shakiness over all previous trials, the computer would smooth out their visual feedback, so that the resultant path of the cursor on the screen would resemble their average. If their path was similar to or better than their average, the computer would leave it unchanged. Unbeknown to the participants, the visual feedback was in fact always smoothed out by a factor of 3, i.e. each x coordinate was divided by 3 ("smooth" condition). A distortion factor of 3 was chosen so as to make it strong enough to have an effect, but at the same time not too extreme so as to be disbelieved. After 20 such trials, the smoothing out was removed, without informing the participants and another 10 such baseline trajectories were performed ("baseline post" condition). There were three groups: 23 functional tremor patients, 23 healthy controls and 22 patients with an organic tremor.

Analysis

A mixed model ANOVA with group as between-subject factor and condition as within-subject factor was performed. The conditions were the average path lengths (or duration) before, during and after the smoothing out of the feedback.

The comparisons of interest were the main effect of condition, indicating whether the condition itself had any effect on the tremor, regardless of the group; and the group x condition interaction, answering the question as to whether there was a difference between the groups in their response to the different conditions. Given the repeated measures design, the respective *p*-value was adjusted using Greenhouse-Geisser's ε.

Both the path lengths and the durations of the trajectories were analysed.

The underlying assumptions of normality and homogeneity of variance were checked.

In view of the large variability in path length and hence duration due the presence of very mild to moderate/severe tremor in the patient groups, it was unlikely that the assumptions of homogeneity

of variance would be met. If they were not, the outcomes were attempted to be normalised by z-scoring: each individual trial was z-scored according to the subject´s overall mean and standard deviation of all trials performed on the same day:

$$\text{z-scored path length} = \frac{\text{pathlength} - \text{mean}}{\text{standard deviation}}$$

The equivalent z-scoring was applied to the durations.

4.2.2.2 Results

All conditions ("baseline pre" "smooth" & "baseline post")

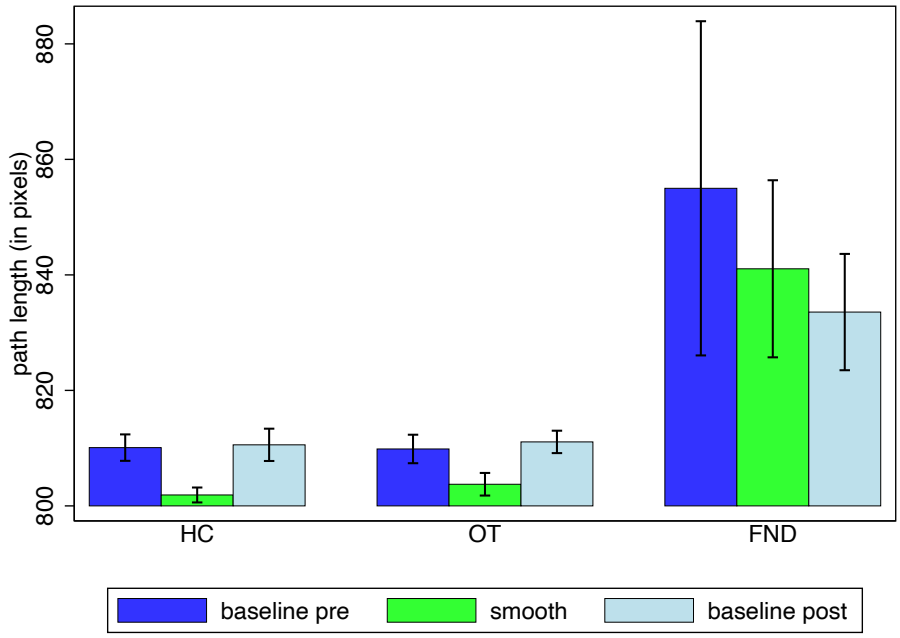


Figure 71: Path lengths before, during and after the smoothing out of the feedback (raw data)
The group mean path lengths for the three conditions are shown. Note that the direct path is 792.5 pixels long. The error bars indicate the standard error of the mean.

	Shapiro-Wilk normality test (*p*-values)		
	Baseline pre	Smooth	Baseline post
HC (n=23)	**.024**	.36	**.049**
OT (n=22)	**.00016**	**.0085**	.060
FND (n=23)	**< .0001**	**< .0001**	**< .0001**
Levene	***p* = .0054**	***p* = .0021**	***p* = .015**

Table 71: Shapiro-Wilk and Levene's test for the path lengths (raw data)
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

As can be seen in Table 71, all but two of the combinations between group and conditions rejected the hypothesis of normality for the raw data and the variance between the groups was unequal in all three conditions.

For the z-scored data on the other hand (Table 72), all but one of the nine combinations between group and condition could be assumed to be normally distributed, and there was no significant difference between the variances for the baseline pre and the baseline post data. Thus, the z-scored data mostly fulfilled the assumptions of a mixed model ANOVA.

	Shapiro-Wilk normality test		
	Baseline pre	Smooth	Baseline post
HC (n=23)	.13	.43	**.010**
OT (n=22)	.069	.71	.39
FND (n=23)	.10	.056	.87
Levene	$p = .053$	$\mathbf{p = .0044}$	$p = .63$

Table 72: Shapiro-Wilk and Levene´s test for the path lengths (z-scored data)
The results of the Shapiro-Wilk normality test are highlighted in blue, those of Levene´s test of homogeneity of variance in purple. Significant results are in bold.

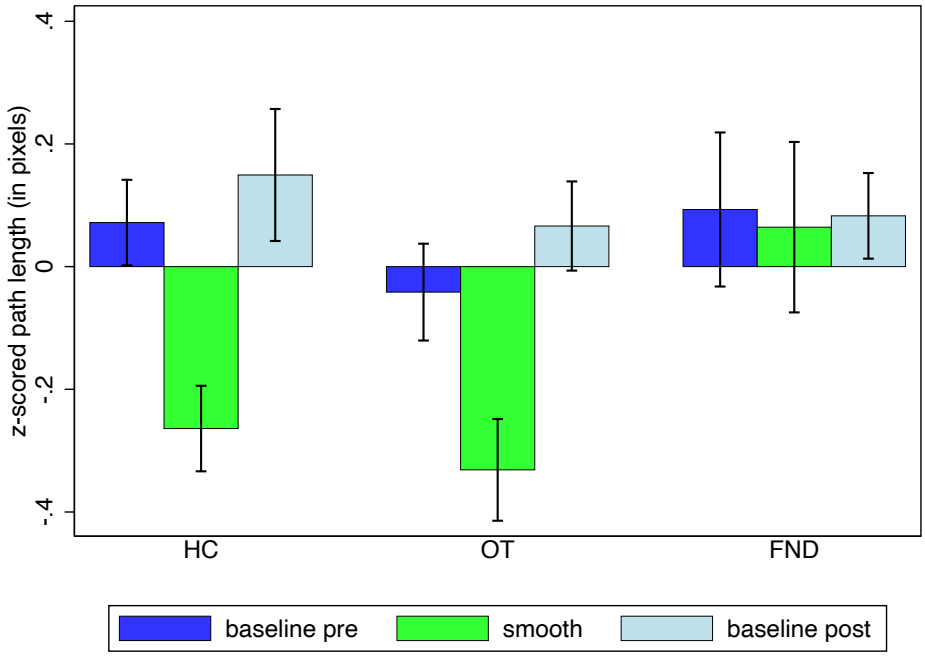


Figure 72: Path lengths before, during and after the smoothing out of the feedback (z-scored data)
The group averages for the three conditions are shown. The error bars indicate the standard error of the mean.

In the mixed model ANOVA of the z-scored data, the main effect of condition was significant (GG $F(2,130) = 8.32$, $p = .0005$). The interaction effect condition x group was not significant (GG $F(4,140) = 1.78$, $p = .14$). Looking at Figure 72 it seems that smoothing out the visual feedback,

made the trajectory straighter in the two control groups, while the smoothing out was still ongoing. Indeed, a post-hoc one-sample t-test on the difference between z-scored data of the "baseline-pre" and "smooth" conditions was significant for both control groups (HC: $t(22)=4.01$, $p = .0006$ (after Šidák-Holm correction $p = .0018$), Cohen´s $d = 0.84$; OT: $t(21)=2.46$, $p = .023$ (after Šidák-Holm correction $p=. 045$), Cohen´s $d = 0.52$), but not for the FND group ($t(22)=.19$, $p = .85$, Cohen´s $d = 0.04$). Wilcoxon matched-pairs signed-rank test performed on the raw data, gave similar results (HC: $z= 3.53$, $p = .0004$ (after Šidák-Holm correction $p= .0013$, $r = .74$, OT: $z = 2.19$, $p = .028$ (after Šidák-Holm correction $p= .056$, $r = .47$, FND: $z = 64$, $p = .52$, $r = .13$)

For the durations raw data, only one out of the nine combinations of group and condition was normally distributed and none of the variances were homogeneous between the groups (Table 73). After z-scoring the data, none of the organic tremor group nor the post baseline condition in the healthy control group were normally distributed and the variance for the baseline-pre condition could not be assumed to be homogeneous between groups (Table 74). The assumptions of the mixed model ANOVA were therefore not met.

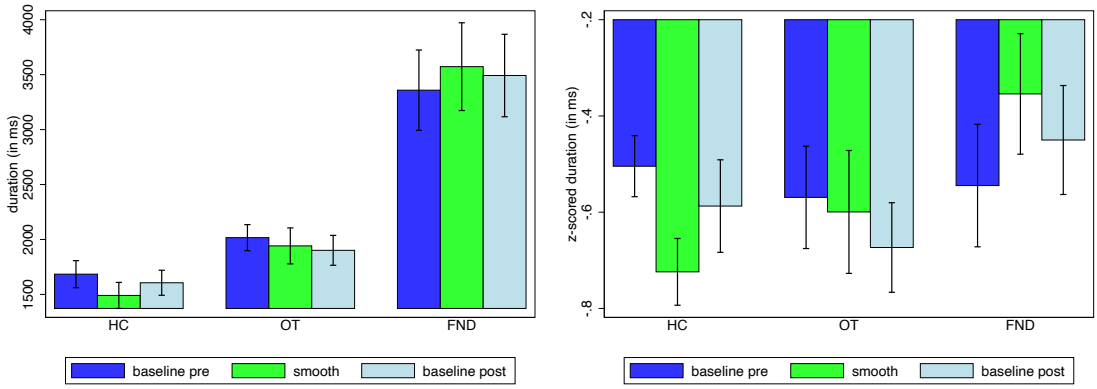


Figure 73: Durations before, during and after the smoothing out of the feedback
The left panel shows the raw data, the right the z-scored data. The results are shown separately for the three groups. The error bars indicate the standard error of the mean.

	Shapiro-Wilk normality test		
	Baseline pre	Smooth	Baseline post
HC (n=23)	**.0070**	**.025**	**.0034**
OT (n=22)	.49	**.0096**	**.036**
FND (n=23)	**.00067**	**.0053**	**.0047**
Levene	***p* = .0014**	***p* = .00038**	***p* = .0018**

Table 73: Shapiro-Wilk and Levene´s test for the durations (raw data)
The results of the Shapiro-Wilk normality test are highlighted in blue, those of Levene´s test of homogeneity of variance in purple. Significant results are highlighted in bold.

	Shapiro-Wilk normality test		
	Baseline pre	Smooth	Baseline post
HC (n=23)	.79	.62	**.014**
OT (n=22)	**.027**	**.00005**	**.00045**
FND (n=23)	.79	.23	.055
Levene	***p* =.044**	*p* = .18	*p* = .35

Table 74: Shapiro-Wilk and Levene´s test for the durations (z-scored data)
The results of the Shapiro-Wilk normality test are highlighted in blue, those of Levene´s test of homogeneity of variance in purple. Significant results are highlighted in bold.

A repeated-measures ANOVA of the path length of the three conditions in the FND group was not significant (GG $F(2,44) = 0.98$, $\eta_p^2 = .043$, $p = .34$)

The importance is not so much what happens while the visual feedback is being smoothed out, but whether or not this effect carried over, when the improved visual feedback was no longer present. The baseline before and after the improved feedback were therefore compared.

Baseline before versus baseline after the improved feedback

The path lengths before and after the smoothing out of the visual feedback were not significantly different in any of the groups (see Table 75).

	Baseline pre	**Baseline post**	**Wilcoxon signed-rank test**
Path length mean (*sd*) (median) in pixels			
HC (n=23)	810 (11.0) (808)	811 (13.4) (808)	Z = -0.52, r = -.11 p = .61
OT (n=22)	810 (11.6) (806)	811 (9.1) (809)	Z = -0.93, r = -.20 p = .35
FND (n=23)	855 (138.8) (814)	834 (48.3) (816)	Z = 0.09, r = .02 p = .93
Duration mean (*sd*) (median) in ms			
HC (n=20)	1684 (591) (1522)	1606 (547) (1444)	Z = 1.58, r = .33 p = .11
OT (n=19)	2017 (556) (1953)	1901 (638) (1701)	Z = 1.9, r = .40 **p = .058**
FND (n=17)	3359 (1753) (3054)	3492 (1800) (3422)	Z = -1.16, r = -.24 p = .25

Table 75: Baseline pre versus post smoothing out of the visual feedback

In the mixed model ANOVA with group as between-subject factor and condition as within-subject factor, the comparisons of interest, namely the main effect of condition and particularly the interaction of group x condition were not significant when analysing the z-scored data of the path lengths (condition: $F(1,65) = 0.81$, $\eta_p^2 = .012$, $p = .37$, group x condition $F(2,65) = 0.30$, $\eta_p^2 = .009$, $p = .74$).

In summary, there was no significant difference between the baseline condition before and after the improved visual feedback in either group, neither in terms of path length nor duration.

4.2.2.3 Interim discussion

Even though the trajectories become straighter while the feedback was being improved in the two control groups, this effect was not significant in the FND group, and even in the control groups did not carry over or persist when the improved feedback was no longer present. This study does therefore not provide any evidence in favour of, nor against using distorted feedback to improve organic or functional tremor. It is possible that the feedback modification was not applied for long enough, or that its intensity was not adequate.

The question therefore remains unanswered, as to whether giving an improved feedback could change patients' beliefs about the severity of their symptoms and therefore improve them. If so, then the recent advances in virtual reality could be harnessed as treatment modalities. The opposite could, however, also be true. If the movement is abnormal, but the visual system feeds back that the movement is normal and that the outcome is good, this may lead to a relearning process in which the abnormal movement is set as the norm. Indeed, clinical experience shows that patients with fixed functional dystonia, can see and know that their limb is in an abnormal position, but with their eyes closed, they perceive it as being in a normal, straight position. Future, carefully planned experiments therefore need to be performed, before applying this type of virtual reality techniques to functional movement disorders.

Changing visual feedback is one way of changing beliefs. Another way is through suggestion, which will be discussed in the next section.

4.3 Placebo

4.3.1 Placebo response in FND

As noted in (1.2.3.1) patients with functional neurological disorders can have strong placebo responses, leading at times to complete symptom resolution, even after years of illness. The aim is to clarify whether functional neurological disorder patients do indeed have a stronger placebo response than controls, or if their strong clinical placebo responses require an explanation other than suggestibility.

In order to attempt to answer this question I performed a classic placebo experiment with an additional conditioning and open-label component and compared the responses of functional neurological disorder patients to those of healthy controls.

4.3.1.1 Methods

Participants

Thirty-two patients with a functional neurological disorder (FND), predominantly movement disorders, and 31 age and gender matched healthy controls took part in the experiment. Two patients and one control subject were excluded (see below under exclusions). Table 76 details the characteristics of the 60 remaining study participants. Note that the resulting slight difference in mean age is not statistically significant (two-sample t-test $t(58)=-0.91$, $p = .37$).

	FND (n=30)	Healthy control (n=30)
M:F	13:17	13:17
Age: average (range)	47.1y (21-79y)	43.7y (21-79)
FND type	• Functional tremor: • Upper limb: 23 • Lower limb: 6 • Head: 1 • Palate: 1 • Functional weakness: 7 • Functional dystonia: 6 • Functional gait disorder: 6 • Functional chronic pain: 5 • Paroxysmal FMD: 4 • NEAD: 4 • Functional myoclonus: 2 • Functional stiffness: 2 • Episodic/transient sensory loss: 2 • Foreign accent syndrome: 1 • Functional diplopia: 1 • Functional sensory disturbance: 1 • Concentration difficulties: 1	• none: 30
Analgesic medication taken daily	• Paracetamol: 2 • NSAIDs: 1 • Tricyclic antidepressant: 2 • SNRI antidepressant: 1 • Antiepileptics: 6 • Non-morphine opioid: 4 • Morphine-like opioid: 2	• Tricyclic antidepressant: 1 • SNRI antidepressant: 1

Table 76: Study participant characteristics
Twenty-one patients had more than one FND type and six took more than one analgesic. "Functional gait disorder" means that the gait disorder comprised a functional gait component not explained by any other listed FND type. NEAD=non-epileptic attack disorder. Antiepileptic medications were gabapentin, pregabalin or carbamazepine.

Nine FND patients (27%) were on a regular analgesic, half of which included an opioid. This contrasted to only two healthy controls (7%) taking antidepressants.

Experimental setup

Four small surface electrodes, with conductive gel, were attached to the subject's forearm with easily removable tape. Two electrodes (cathode and anode) were attached to the medial forearm, two to the lateral forearm. This ensured that the two sites were innervated by different nerves and located in different dermatomes. Functional sensory symptoms often accompany functional movement disorders and tend to be more marked ipsilaterally to the movement disorder. So as to

avoid this possible confounder, both electrodes were placed on the same arm, always on the asymptomatic or less symptomatic side.

The stimulus was a single, 200 microsecond biphasic electric pulse, administered by a DS8R Digitimer® device. So as to hide the intensity changes from the participant, this device was driven by a Matlab® program, with the help of a National Instruments Data Acquisition device. Subjects were always warned about the next stimulus by a countdown ("3,2,1"). Participants were reminded that they could interrupt the experiment at any time if they wished to.

The sequence of events was the following:

1. *Pain threshold & maximum intensity determination*

   Starting with a 2mA intensity, the stimulus intensity was increased in 1mA steps, until it was perceived as slightly painful. This was noted as the pain threshold. In subjects who did not perceive the 2mA stimulus, the sensory threshold was also determined.

   The intensity was further increased in steps of 1mA, followed each time by a pain rating on a scale from 0 (no pain) to 10 (worst possible pain). The intensity was increased until a mild to moderate pain level was achieved, that was easily tolerated, and did not exceed 40mA. The reached intensity was the "maximum" intensity for this individual. The same procedure was repeated on the second site, aiming for a similar pain rating for its "maximum" intensity. Which of the two sites was the placebo and which the control site was randomly allocated.

   Given functional neurological disorders are often triggered by minor physical trauma (see 1.1), care was taken not to administer too high an intensity to any patient and as a consequence to any of the controls. The stimulation intensity was kept below 41mA and the intensity was not increased any further or even slightly diminished when the stimulus became a bit too painful for the subject. Therefore, given subjects' pain ratings varied widely, no fixed number on the rating scale was aimed for and the intensities used and the pain ratings given, varied between subjects.

2. *Baseline pain threshold & maximum intensity rating*

   Starting at 2mA, the stimulus intensity was increased in 1mA steps until the stimulus was perceived as very slightly painful ("pain threshold"). So as to make the intensity unpredictable, each new stimulus was either of the same intensity as the previous one or 1mA higher. Subsequently, the previously established maximum intensity (see point 1) was applied and rated three times. The same was repeated for the 2nd site.

3. "Anaesthetic" and face-cream administration

The electrodes were removed and an "anaesthetic" cream stored in a small white container was applied to the "anaesthetised" site and a standard face-cream stored in a larger white container was applied to the control site. The subject was told that the anaesthetic cream would decrease their pain sensation. In reality, both creams were the same face-cream.

4. 10 min wait

The subject was told that the anaesthetic cream needed ten minutes to take its effect. Following this interval, the creams were removed and the electrodes reapplied on the same locations.

5. Post-cream pain threshold & maximum intensity rating

The procedure of point 2 was repeated: the pain threshold was determined and the maximum intensity was rated three times at both sites.

6. 5 min wait

The subject was told that another five minutes would be given for the anaesthetic cream to take its effect. It was explained that while the anaesthetic cream had been wiped off, it had gone into the skin, and needed to reach the nerve so as to be effective.

7. Conditioning stimulus

The subject was told that a single maximum pulse would be administered to both sites so as to evaluate if the extra wait had been beneficial. The maximum intensity was administered on the control side, but unbeknown to the participant, only half the maximum intensity was administered on the "anaesthetised" site. This conditioning stimulus was meant to reinforce the belief that the anaesthetic cream was effective. The subject rated the pain and given the lower rating, the examiner reinforced the fact that the anaesthetic cream was effective.

8. Post conditioning threshold & maximum intensity rating

As before, the pain threshold was determined, and the maximum intensity was rated three times. Beforehand, I reinforced the belief that the anaesthetic cream was effective by a casual comment of the type of: "I will now give you the maximum intensity again, but you've obviously had the anaesthetic cream which is working well."

9. Full disclosure

I told the participant that I had a confession to make and asked them to guess what it was. I fully disclosed the fact that the creams were identical face-creams, and that the decreased pain sensation was due to a placebo effect. They were explicitly asked if they had believed that the applied cream was an anaesthetic cream or if they had thought it was a placebo. I explained the reasons for doing this experiment (see introductory note) and answered all questions in a completely transparent manner. I briefly explained that deceptive placebo use is prohibited in clinical practice in the UK, but that some studies advocated the use of open-label placebo. I explained that open label placebo could work if the power of placebo was explained to patients and strong positive suggestion used. I explained that this was not strictly speaking open-label placebo, but that now they knew that the two creams were face-creams, we would repeat the same thing as an approximation to open-label placebo. I explained that they might still feel less pain on the placebo site, as the brain might have learned that the placebo site was less painful.

10. Post-disclosure threshold & maximum intensity rating

Knowing the nature of the creams, the pain threshold was determined again, and the maximum intensity rated three more times at each site.

Exclusion

Since the patient information sheet read: “We might also apply a strong painkiller / anaesthetic cream, an inactive cream or a placebo so as to evaluate their effects.”, it was decided in advance to exclude anyone stating they had not believed that one of the applied creams was an anaesthetic. Two patients (one who thought that the “anaesthetic” cream was a placebo, and one who thought the two creams had been inverted) and one healthy control (did not engage in the task) were excluded from all analyses. This left 30 participants in each group.

4.3.1.2 Results

4.3.1.2.1 Pain ratings

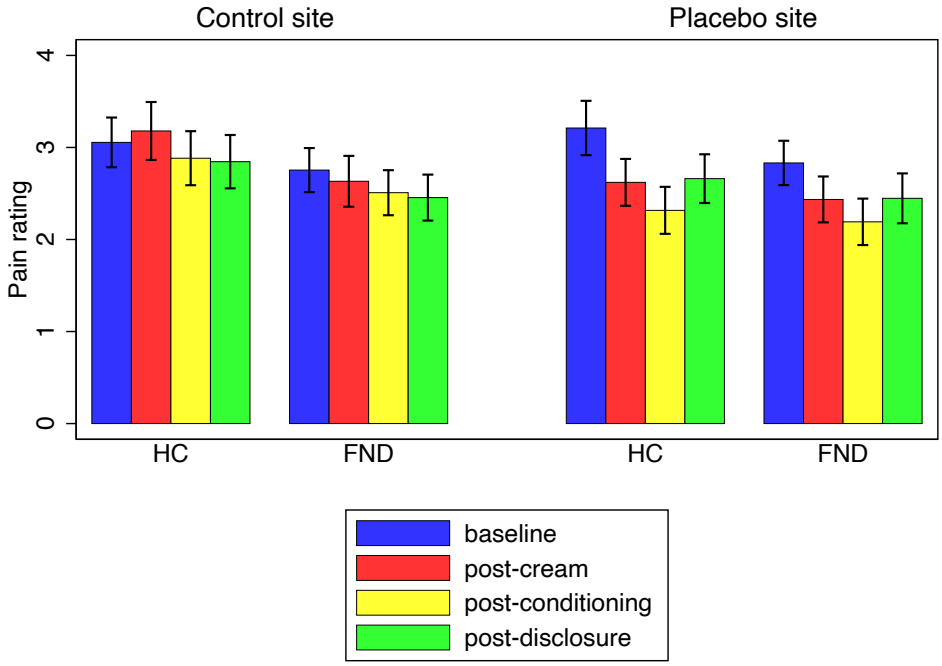


Figure 74: Pain ratings in the different conditions at the control and placebo sites
The group average pain ratings, on a scale from 0 to 10 are depicted for the four different conditions at the control and the placebo site, both for healthy controls (HC, n=30) and functional movement disorders patients (FND, n=30). The error bars indicate the standard error of the mean.

Part of the decrease in pain rating can be attributed to adaptation to the stimulus over time. This adaptation can be seen on the control site, particularly in the FND group, in which the pain rating of an identical stimulus mildly but gradually decreases over time. Note that the slight difference between the baseline and post-cream pain rating on the control site in the control group is not statistically significant (paired t-test: p = .27, CI -0.33482 0.1003). In order to remove the adaptation component, the difference between the control and placebo sites are shown in Figure 75.

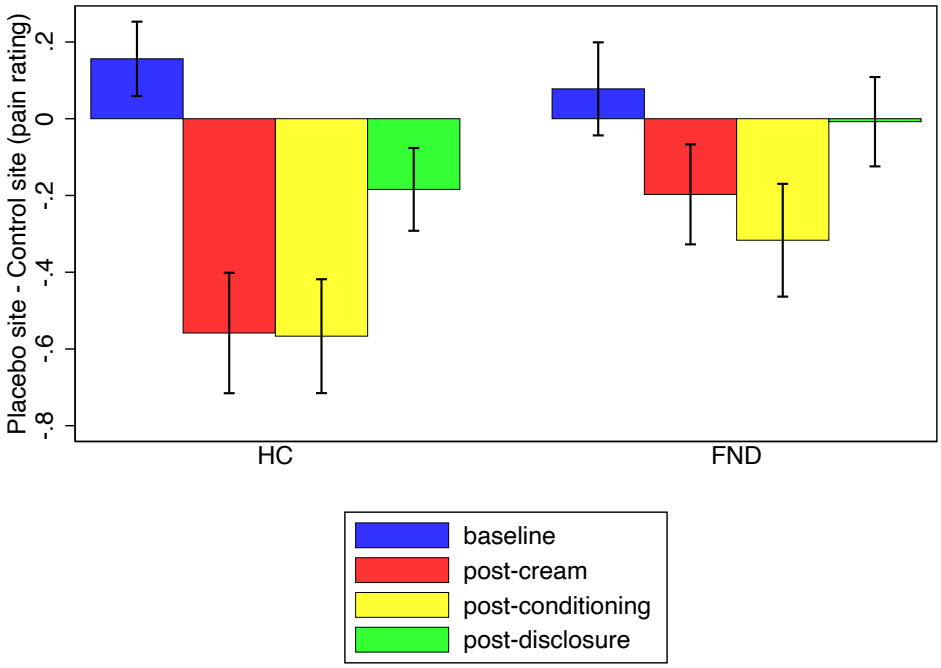


Figure 75: Differences in pain ratings at the placebo and control sites
For each condition the pain rating at the control site is subtracted from the pain rating at the placebo site. A resulting negative difference means the placebo site was less painful than the control site, indicating a placebo effect. The error bars indicate the standard error of the mean. There were 30 HC and 30 FND patients.

Assumptions check

	Shapiro-Wilk normality test							
	Control site				Placebo site			
	Baseline	Post-cream	Post-conditioning	Post-disclosure	Baseline	Post-cream	Post-conditioning	Post-disclosure
HC	0.34	0.83	0.39	0.54	0.77	0.70	0.13	0.62
FND	0.62	0.44	0.70	0.27	0.45	0.86	0.20	0.46
Levene	0.54	0.47	0.32	0.48	0.19	0.71	0.59	0.93

Table 77: Shapiro-Wilk and Levene´s test for the pain ratings
The results of the Shapiro-Wilk normality test are highlighted in blue, those of Levene´s test of homogeneity of variance in purple. None of the results are significant.

Effects

In order to evaluate the effect of the placebo cream, the additional conditioning stimulus and the open-label placebo effect after full disclosure, the respective pain ratings were analysed by means of a 3-way mixed model ANOVA. Given the normal distribution of the data and the absence of unequal variances between groups, the underlying assumptions were met (Table 77). Group was the between-subject factor and there were two within-subject factors: the site (placebo or control site) and the condition (the two respective conditions being compared). Both condition and site

were repeated measures and the dependent variable was the average of the three pain ratings given for each condition at each site. The effects of interest were the following:

- interaction of site and condition, i.e. did the pain rating vary between the two conditions according to whether it was tested at the control or placebo site. This allowed for example to exclude that a decrease in pain rating was simply due to adaptation over time.
- interaction of site x condition x group, i.e. was there a difference between the two groups with regards to the above interaction

Given the repeated measures design, the assumption of sphericity was checked in each case but did not require any adjustment using Greenhouse-Geisser's ε.

Baseline

So as to exclude any difference between the groups and sites at baseline, the baseline ratings were compared. A two-way mixed model ANOVA of only the baseline conditions with group as between-subject factor and site as within-subject factor, did not show any significant difference across the two sites nor the two groups, indicating that the baseline pain ratings were not dissimilar at the control and placebo sites nor between patients and healthy controls (site: $F(1,58) = 2.27$, $\eta_p^2 = .038$, $p = .14$, group: ($F(1,58) = 0.88$, $\eta_p^2 = .015$, $p = .35$, site x group interaction: ($F(1,58) = 0.25$, $\eta_p^2 = .004$, $p = .62$).

Post-cream versus baseline condition

This comparison shows any placebo effect induced by the placebo cream. There was a significant interaction of site and condition ($F(1,58) = 16.86$, $\eta_p^2 = .23$, $p = .0001$), indicating that the pain rating for the two conditions significantly differed at the placebo and control sites. Inspection of the raw data (Figure 74 and Figure 75) made it clear that there was a reduction in pain following the administration of the placebo cream, but not following the control cream. There was a trend for this interaction to differ between the two groups (group x site x condition interaction ($F(1,58) = 3.33$, $\eta_p^2 = .054$, $p = .073$), i.e. there was a trend for the placebo effect to be less marked in the functional group compared to healthy controls. (HC decrease in pain rating: 0.590, FND decrease in pain rating: 0.397).

Post-conditioning versus baseline

This comparison evaluates the combined effect of the placebo cream and the conditioning stimulus. There was a significant site x condition interaction ($F(1,58) = 20.85$, $\eta_p^2 = .26$, $p = < .0001$). Inspection of the data (Figure 74 and Figure 75) showed that the combined placebo and conditioning effect decreased the pain rating on the placebo site but not the control site. This

effect was not dissimilar in the two groups (the group x site x condition interaction was not significant ($F(1,58) = 1.80$, $\eta_p^2 = .030$, $p = .18$).

Post-conditioning versus post-cream

This comparison looks particularly at the effect of the conditioning stimulus, but some of its effect also needs to be attributed to the placebo cream, since the subjects were told that the extra wait would enhance the cream´s anaesthetic effect.

The additional five-minute wait and the conditioning stimulus did not significantly decrease the pain rating further than the placebo cream on its own (site x condition ($F(1,58) = 0.50$, $\eta_p^2 = .0085$, $p = .48$). Although looking at the raw data (Figure 74), one could see a further decrease, particularly in the FND group, this was not significantly different from the decrease that could be attributed to likely adaptation which was also seen in both groups on the control site. There was also no significant difference in this effect between the two groups (group x site x condition ($F(1,58) = 0.38$, $\eta_p^2 = .0064$, $p = .54$).

Post-disclosure versus post-conditioning

Disclosing to the participant that the cream was in fact a placebo cream lead to a subsequent increase in the pain rating on the placebo site (site x condition $F(1,58) = 14.54$, $\eta_p^2 = .20$, $p = .0003$) (see Figure 74 and Figure 75)). This was the difference between the combined deceptive placebo effect and conditioning effect and the remaining placebo effect post disclosure (open-label placebo effect following experience and disclosure of deceptive placebo and conditioning).

There was no significant difference for this effect between the two groups (group x site x condition ($F(1,58) = 0.16$, $\eta_p^2 = .0028$, $p = .69$).

Baseline versus post-disclosure

There was a significant site x condition effect ($F(1,58) = 5.32$, $\eta_p^2 = .084$, $p = .025$), but not group x site x condition effect ($F(1,58) = 1.90$, $\eta_p^2 = .032$, $p = .17$) when comparing the baseline pain rating to the pain rating following the disclosure. This difference can be interpreted as the open-label placebo effect following the experience and disclosure of a deceptive placebo effect and of a conditioning effect.

Considerations

The disadvantage of an ANOVA is that the averages of the three repetitions are used instead of each individual datapoint. Since the maximum stimulus was rated three times at each condition and site, three stimuli were applied at the same location in close temporal succession. It was

expected that the pain rating of the identical stimuli would increase from one stimulus to the next in this succession of three stimuli, and indeed it did so in a linear manner (Figure 76).

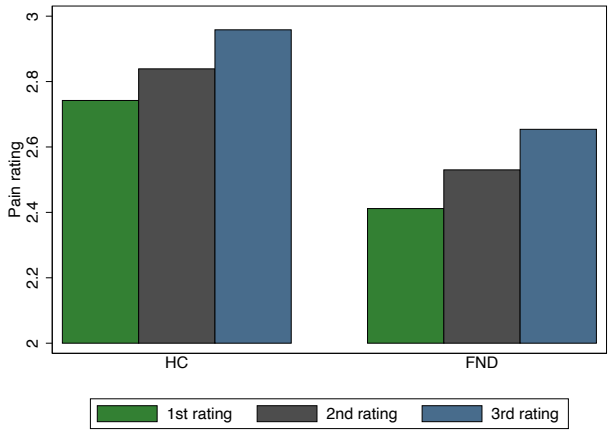


Figure 76: pain ratings according to repetition
Pain ratings of all conditions across both sites, according to whether it was the 1st, 2nd or 3rd pain rating within the triad.

Performing a 4-way ANOVA with repetition as an additional within factor, gives a statistically significant main effect of repetition in every comparison, but obviously does not change the results of the other main effects or interactions. Using a model that accounts for this variability caused by the repetition effect, lead to a more powerful test. Hence a linear mixed effects model approach was used. Its results are detailed in appendix A 9.1. In summary, the linear mixed effects analysis gives the same significant results as the mixed ANOVA, but in addition also gives a significant group x site x condition interaction for the post cream versus baseline condition (p = .0041) and for the post-conditioning versus baseline condition (p = .042). Thus suggesting, that what only appeared as a trend in the mixed ANOVA was in fact highly significant: FND patients had a smaller placebo effect than healthy controls. The issue with the linear mixed effects model is that the residuals are dissimilar between subjects, meaning the assumptions of the linear mixed effects model are not entirely met. In addition, these significant group x site x condition interactions disappear when the raw data is normalised by z-scoring or by transforming it into a percentage of the first baseline ratings across both sites. It is therefore more cautious to ignore the additional significant results of the linear mixed effects model and rely the ones of the mixed model ANOVA, which are robust and persist even with normalisation of the data.

4.3.1.2.1 Pain thresholds

The same mixed ANOVA comparisons as for the maximum intensity pain ratings were performed for the pain thresholds. None of these were statistically significant. This is not surprising, since placebo effects are generally seen with higher intensity pain than threshold levels.

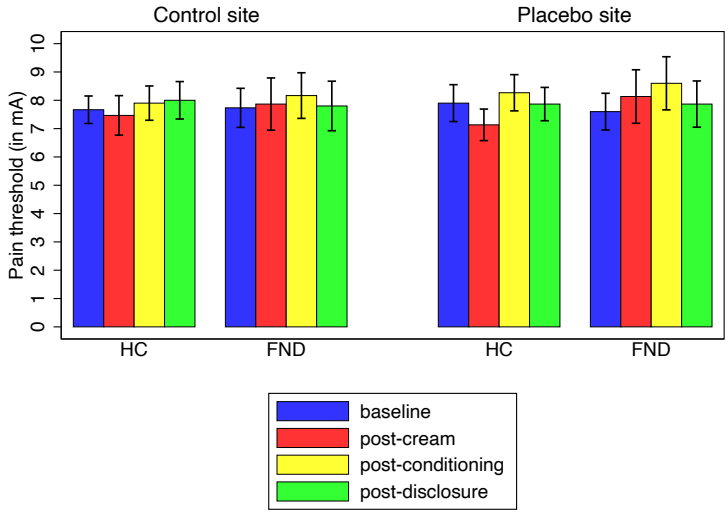


Figure 77: Pain thresholds in the different conditions at the control and placebo sites
The group average pain thresholds, on a scale from 0 to 10 are depicted for the four different conditions at the control and the placebo site, both for healthy controls (HC, n=30) and functional movement disorders patients (FND, n=30). The error bars indicate the standard error of the mean.

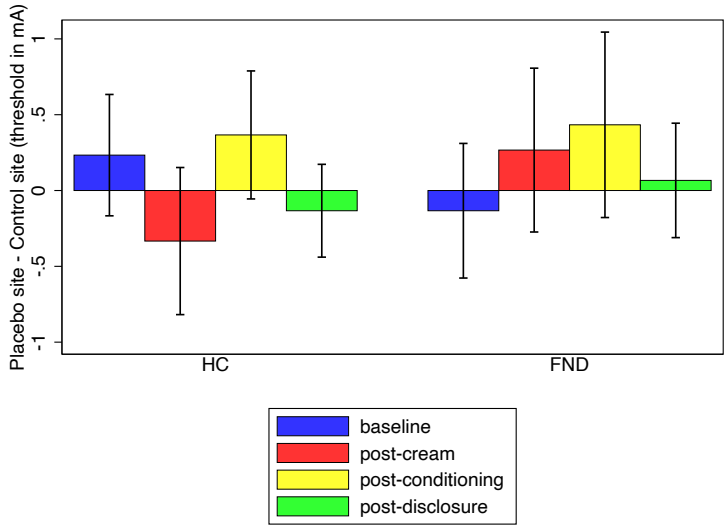


Figure 78: Differences in pain thresholds at the placebo and control sites
For each condition the pain threshold at the control site is subtracted from the threshold at the placebo site. A resulting positive difference means the placebo site was less painful than the control site, indicating a placebo effect. The error bars indicate the standard error of the mean. There are 30 HC and 30 FND patients.

	Shapiro-Wilk normality test							
	Control site				Placebo site			
	Baseline	Post-cream	Post-conditioning	Post-disclosure	Baseline	Post-cream	Post-conditioning	Post-disclosure
HC	0.29	**0.023**	0.69	0.63	0.65	0.72	0.70	0.13
FND	0.25	**0.0004**	**0.0012**	**0.0005**	0.60	**0.003**	**0.00007**	**0.024**
Levene	0.11	0.39	0.62	0.69	0.88	**0.028**	0.41	0.065

Table 78: Shapiro-Wilk and Levene´s test for the pain thresholds
The results of the Shapiro-Wilk normality test are highlighted in blue, those of Levene´s test of homogeneity of variance in purple. Significant results are highlighted in bold.

4.3.1.2.2 Stimulus intensity and pain rating

Interestingly, the average pain ratings in the FND group were significantly lower than in the healthy control group, despite there being a trend for the stimulus intensities used in the FND group to be higher (Table 79).

	Stimulus intensity (in mA)	**Pain rating** (range 0-10)
HC (n=30)	21.4	2.85
FND (n=30)	24.4	2.53
Two-sample t-test	p = .0529	**p< .0001**
CI	[-6.14, 0.04]	[0.162, 0.468]

Table 79: Stimulus intensity and pain rating group averages
Group averages of the stimulus intensities in mA on the placebo and control site with the overall average of all pain ratings.

Could the difference be explained by the higher analgesia use in the FND group (see Table 76)? Excluding the nine FND patients and the two healthy controls who were taking regular analgesic medication, does not change this pattern, on the contrary, the difference in stimulus intensity between the two groups now becomes statistically significant and the difference in pain rating remains statistically significant (see Table 80).

	Stimulus intensity (in mA)	**Pain rating** (range 0-10)
HC (n=28)	21.0	2.81
FND (n=21)	25.6	2.51
Two-sample t-test	***p* = .0102**	***p* = .001**
CI	[-8.12, - 1.12]	[0.120, 0.480]

Table 80: Stimulus intensity and pain rating group averages (excluding all subjects on analgesic medication)
Group averages of the stimulus intensities in mA on the placebo and control site with the overall average of all pain ratings. Only including subjects who were on no regular analgesic medication and hence had not taken any analgesic on the day of the study.

Thus, the higher intensity coupled with the lower pain rating in the FND compared to the healthy controls cannot be explained by the increased analgesic use. Age is not significantly different between the two groups and therefore cannot be the explanatory factor.

Since the lowest intensity the apparatus could deliver was 2mA, the exact sensory threshold could not be determined. However, only 13% (4/30) of FND patients failed to perceive the 2mA stimulus on at least one site and so did 3 % of healthy controls.

Nine FND patients had a pain condition (organic or functional), one patient had a sensory anomaly (perceiving every sensory stimulus, regardless of type, twice). These subjects with a pain condition were unsurprisingly the same subjects as the ones taking regular analgesic medication with the exception of three subjects (1 FND, 2 HC) who took antidepressant medication not for pain relief but for a mood disorder and one subject who had chronic pain but was on no regular medication.

Excluding subjects with either a pain condition or a chronic sensory abnormality still showed a significant difference in pain rating between the two groups.

	Stimulus intensity (in mA)	**Pain rating** (range 0-10)
HC (n=30)	21.4	2.85
FND (n=20)	24.2	2.67
Two-sample t-test	*p* = .103	***p* = .045**
CI	[-6.29, 0.59]	[-0.0044, 0.358]

Table 81: Stimulus intensity and pain rating group averages (excluding all subjects with a chronic sensory or pain condition)
Group averages of the stimulus intensities in mA on the placebo and control site with the overall average of all pain ratings. Only including subjects who did not have any chronic pain or sensory condition.

Although the stimulus intensity was no longer statistically different between the two groups, the nevertheless slightly higher intensities coupled with a significantly lower pain rating in the FND group indicates that patients with FND have a tendency to underreport pain compared to healthy controls.

4.3.1.3 Interim discussion

The results show that functional neurological disorder patients do not have a stronger placebo response in a standard analgesic placebo experiment than healthy controls. There is even a trend for their placebo response to be less pronounced than in healthy controls following the administration of a placebo cream.

The common notion of functional movement disorders patients being suggestible appears therefore to be incorrect. So why is there an erroneous (on the basis of these data) and stigmatising notion of suggestibility in this patient group? Clinical experience shows that functional symptoms tend to manifest, when they are talked about. It is for example much more common to witness a non-epileptic attack disorder, than an epileptic seizure in an outpatient appointment. These findings have led to the interpretation of suggestibility. Yet, another similarly likely interpretation of symptoms appearing when they are being talked about is that they are strongly influenced by attention. As discussed in 1.1 functional symptoms typically manifest when attention is directed to them and improve or disappear with distraction.

Another reason for the erroneous notion of suggestibility are the occasionally observed impressive placebo responses. How else can they be explained? Functional symptoms are inherently variable and changeable. Functional symptoms can vary from severe to almost asymptomatic and indeed distraction can lead to their transient disappearance. Compare functional leg weakness, with a patient who has suffered a stroke. A placebo effect in a stroke patient can lead to a slight increase in strength, but never to complete symptom resolution because of the physical damage to the motor system. A placebo effect in a wheelchair-bound functional paraplegic patient on the other hand, can lead to complete (but often temporary) recovery. Functional symptoms are much more changeable than organic disorders, explaining why a placebo response can have a much larger effect in functional compared to organic symptoms.

The results also show that open-label placebo, following the experience of deceptive placebo and a conditioning stimulus and following full disclosure of these, is far less effective than the combined deceptive placebo and the conditioning induced placebo effect. Thus, the placebo effect significantly diminishes with disclosure. Nevertheless, compared to the baseline condition, there is a significant placebo effect, which albeit smaller than the deceptive placebo effect is still

present. Given the risks surrounding the use of deceptive placebo in clinical practice, open-label placebo could be used as an ethically acceptable alternative in some patients.

Concerning the intensities used and the average pain rating, functional neurological disorder patients tend to report a lower pain level at equal intensities. This statistically significant difference persists when subjects on analgesic medication are excluded and also when subjects with a chronic pain or sensory condition are excluded. Note that the perceived intensity of the stimulus depends on the exact positioning of the electrodes, the tightness with which they are attached and the presence of any sensory abnormalities. The stimulation sites were nevertheless very similar, and all experiments were performed by myself, thus using the same method. Since the lowest stimulus intensity that could be applied was 2mA, which was felt by the majority of subjects, the exact sensory threshold for each subject could not be determined. A future experiment could investigate exact sensory thresholds and use a method that does not contain the possibility of variation in intensity, e.g. ice-cold water of a fixed temperature. Nevertheless, it can be concluded that FND patients' pain reporting is not higher than that of healthy controls at equal intensities, but instead shows a tendency to slight underreporting. Similar results have been found in patients with functional dystonia, in whom pain thresholds were normal, but pain tolerance was increased (Morgante et al. 2018).

A limitation of this study is that there was no organic patient control group. A possible confounder is the fact that I have been the doctor looking after many of the FND patients and so they might have had more "trust" in me and believed me more than the healthy controls when I told them that I was applying an anaesthetic cream. This concern does, however, not seem justified, since none of the healthy controls disbelieved me, but two FND patients did. Another possible limitation is the differing analgesic use between the two groups, but having each subject serve as their own control, ameliorated this effect.

In summary, FND patients do not have a stronger placebo effect than healthy controls in a standard analgesic placebo experiment. There is even a trend for it to be slightly smaller. The notion of suggestibility in this patient group therefore needs to be challenged and changed.

Future experiment: Nocebo effect

Functional symptoms might in part be linked to a nocebo effect. Patients might dread the symptom appearing so much, that they in fact predict it to happen. As a result, the brain fulfils the predicted movements; akin to a self-predicted prophecy. It would therefore be interesting to evaluate whether the nocebo effect is stronger in patients with FND than in healthy controls.

A very low pain stimulus could be paired with a certain image (e.g. a purple coloured symbol) and a mild to medium pain stimulus with another image (e.g. a yellow coloured symbol) so that the participant forms an association between the image and the pain intensity. A pain rating would be given after each stimulation.

After a while, this association would be reversed, so that the image that previously predicted the very mild pain would now be followed by the mild to moderate pain and vice versa (so called reversal learning). This would allow the study of expectations and also of the nocebo effect (the opposite of a placebo effect): the image that previously indicated the arrival of a mild to moderately painful stimulus would now be followed by a very mild stimulus – if there was a nocebo effect, then the stimulus would be perceived as being more painful even though it was in fact a very mild stimulus.

4.3.2 Survey on the use of placebo treatments in clinical practice

Given the poor prognosis of FND and the frequent lack of availability of treatments, coupled with the occasional dramatic placebo response, one might wonder whether or not placebo treatments should occasionally be used in clinical practice. A survey was therefore performed, asking FND patients, patients with organic symptoms, health-care professionals and healthy controls about their opinion. In addition, healthcare professionals were asked about their current practice.

4.3.2.1 Methods

Questionnaire

The question style was inspired by and in part adapted from previous published surveys, in particular from (Howick et al. 2013; Lim and Seet 2007; Lynoe, Mattsson, and Sandlund 1993; Nitzan and Lichtenberg 2004; Raz et al. 2011).

The patient and healthy controls questionnaire and the healthcare professionals questionnaire are available in appendix A 10.1 and A 10.2 respectively. Alternatively, online versions of the questionnaires can be accessed via the following links:

Patient and healthy controls: https://is.gd/placebosurvey

Healthcare professionals: https://is.gd/hcp_placebosurvey

The results section also contains all the questions.

Simple language was used so as to make it accessible to all levels of education. In order to be able to directly compare the healthcare professionals' answers with those form patients, the phrasing of the questions was identical in both questionnaires.

The questionnaire was preceded by an introduction so as to ensure people understood what placebo treatments are. It is inherently difficult, not to bias people's responses, by the way the introduction or questions are phrased, but every possible effort was made to avoid any bias.

The survey was primarily administered online. Study data were collected and managed using REDCap electronic data capture tools hosted at UCL (Harris et al. 2009, 2019). People who asked for a paper format, were sent a paper version with a stamped return envelope.

Dissemination

In an attempt to reach as large a number as possible, the survey was disseminated by the means listed below. The estimated number of responses is also given. Given the anonymity of the survey, it is impossible to be exact about the number of replies each dissemination method yielded. However, given most people seem to either respond within the first few days or not at all, the timings of the different advertisements allow an approximation.

- Patient organisations:
    - FND Hope
        - The survey was advertised via their Facebook page and Twitter
        - Approximately 35 patients responded
    - FND Action
        - The survey was advertised on their website
    - Dystonia UK London Branch
        - The survey was included in their Autumn 2019 newsletter, which was e-mailed to several hundred people
        - Less than ten patients responded
- Research databases
    - National Institute of Health Research BioResource
        - Sent the survey electronically to 2'000 patients with neurological disorders or functional disorders (conversion disorder).
        - So far it led to approximately 250 replies
        - In this context I gratefully acknowledge the participation of all NIHR UCL BioResource volunteers, and thank the NIHR UCL BioResource centre and staff for their contribution. I thank the National Institute for health research and NHS Blood and Transplant.
    - Queen Square Movement Disorders Centre's Movement Disorders Research Registry
        - 550 movement disorders patients were contacted by e-mail, 64 by postal letter
        - Approximately 150 patients took part in the survey
    - ICNSubject database (UCL institute of cognitive neurosciences)
        - The survey was advertised on this database which contains approximately 300 healthy subjects
        - The response rate seems to have been below 10
- Professional organisations
    - Association of British Neurologists

        - The survey was included in their monthly newsletter, which is sent to all their members neurologists
        - ABNT – it was also included in their newsletters to neurology trainees
    - UKFNS
        - The UK functional neurological society is a closed group of approximately 50 researchers, mostly neurologists and psychiatrists, who are actively involved in FND research
        - Approximately 15 FND specialists responded
- Clinicaltrials.gov
    - Given the ethics committee originally required the research study to feature in Clinicaltrials.gov, this survey was added to it. Only the patients survey was added, so as to prevent the possibility of non-professionals pretending to be healthcare professionals.
- Study participants
    - Study participants of the different experiments described in this thesis, were asked to complete this survey either on the day or they were contacted later
- Colleagues and friends

Exclusion

If a person misunderstood the essence of placebos, their answers became uninterpretable. A question at the end therefore verified if participants had understood the meaning of placebo treatments.

Q12: A placebo pill (select all that apply)

- is an inactive treatment that never improves health issues
- is an inactive treatment that can improve health issues
- works because of the substance it contains
- works because patients believe it will improve their health issues

Anyone who ticked one of the two incorrect answers (1 or 3) was excluded, unless their optional comments made it clear that they had understood the meaning of placebo treatments (The latter was the case in two medical patients and two non-functional neurological patients). A total of 58 subjects had to be excluded (14 FND, 38 organic neurological and 6 medical condition / healthy controls).

4.3.2.2 Results

The answers to each question are shown by means of a pie chart for the neurological patients who do not have a functional disorder ("Neuro"), patients with a functional neurological disorder ("FND") and healthcare professionals. For a better overview, healthy controls and people with non-neurological medical conditions ("HC / Med") are not included in these figures, they can however be found in appendix A 10.3.

The colour scheme helps to get a quick overview: green indicates agreement, red disagreement, bright red means strong disagreement. The percentages are included in the pie charts.

After exclusion there were a total number of

- 96 FND patients
- 246 non-FND neurological patients
- 91 healthy controls or medical non-neurological patients
- 49 healthcare professionals
    - 43 doctors (8 of which were still in specialist training)
    - 6 psychologists or physiotherapists.
    - Twenty were specialists in functional neurological disorders.

While looking at the difference in the responses between the different groups is of some interest, the main question of interest is the overall attitude towards these issues and the percentage who strongly oppose them.

This survey is still ongoing, but the preliminary results are shown below.

Q1: What are your initial thoughts? Do you think doctors should use deceptive placebo treatments if they think their patient could get a beneficial placebo effect from it?

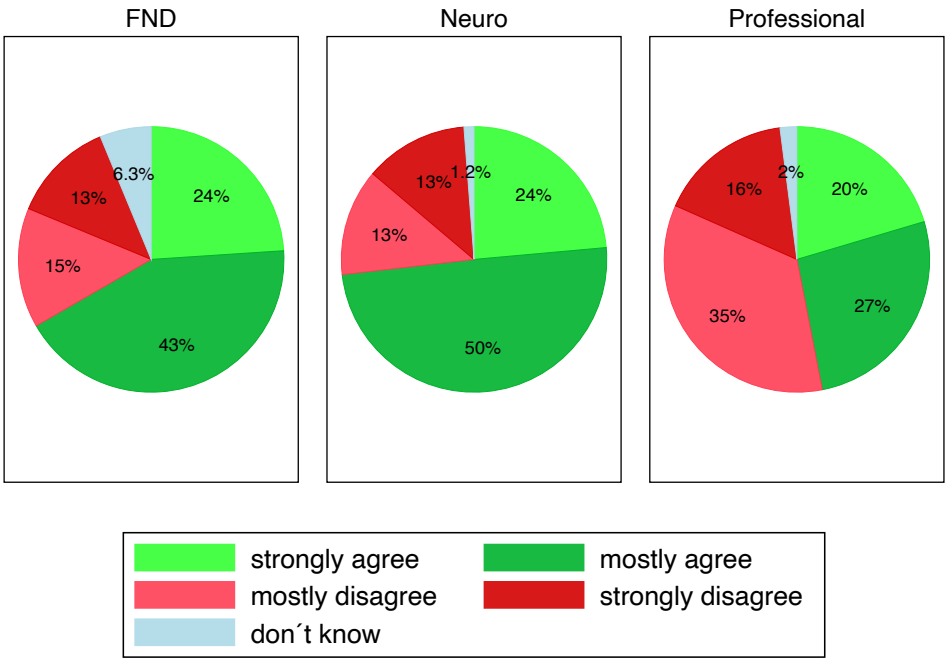


Figure 79: Q1

It is immediately apparent, that healthcare professionals were more opposed to placebo treatments than either patient group. Grouping the agree and the disagree options together and performing a Chi-square goodness of fit test confirmed that the difference was significant (Table 82).

	Agree	**Disagree**
FND (n=90)	71.1%	28.9%
Neuro (n=243)	74.1%	25.9%
Professional (48)	47.9%	52.1%
Chi-square goodness of fit	$\chi^2(2) = 13.14$	
	***p* = .001**	

Table 82: Agree versus disagree

Q2: Do you think a placebo treatment could improve your symptoms?

(If you do not currently suffer from a medical condition, think about a medical problem you have experienced in the past)

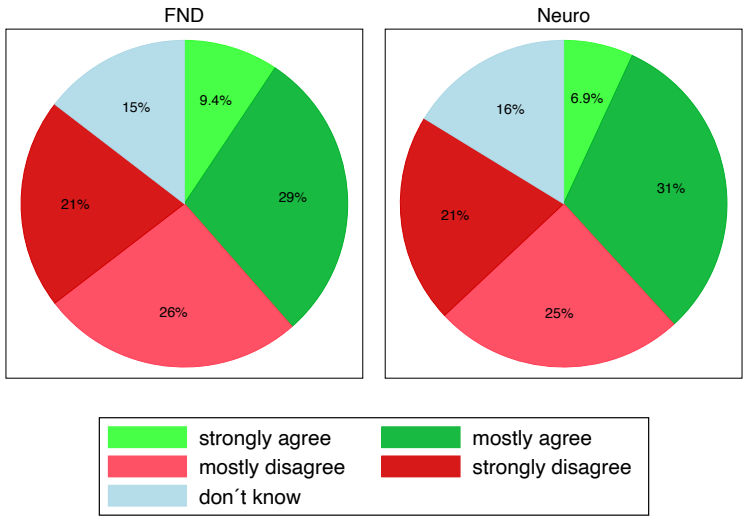


Figure 80: Q2

As can be seen in Figure 80, 38% of patients think that a placebo treatment could improve their symptoms. This number was the same in both patient groups. Healthcare professionals, think that placebos would lead to a clinical benefit in 41% of patients with purely organic symptoms (*sd* =18.4), thus giving a very similar estimate as the neurological patients. However, healthcare professionals estimated that placebos would lead to a clinical benefit in 69% of patients with purely functional symptoms (*sd* =20.6), which was much higher than the FND patients' estimate. Figure 81 shows the spread of the responses.

Q2 for healthcare professionals: In what percentage of patients do you think placebo treatments would lead to clinical benefit with improved measures of symptoms or quality of life?

a) in purely *organic* symptoms **b) in purely *functional* symptoms**

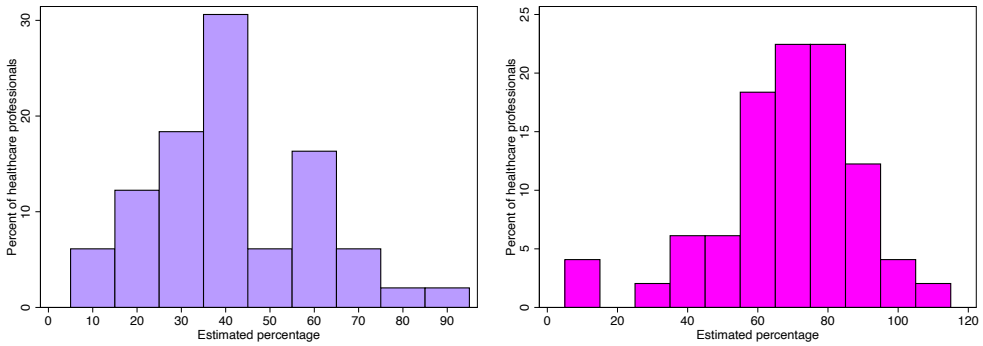


Figure 81: Q2a & b for healthcare professionals

These histograms indicate what percentage of healthcare professionals estimated which percentage.

Q3: Considering potential risks of deceptive placebo treatment, where the patient does not know that the treatment is a placebo:

a) If doctors used deceptive placebo treatments, patients would lose trust in doctors and medicine.

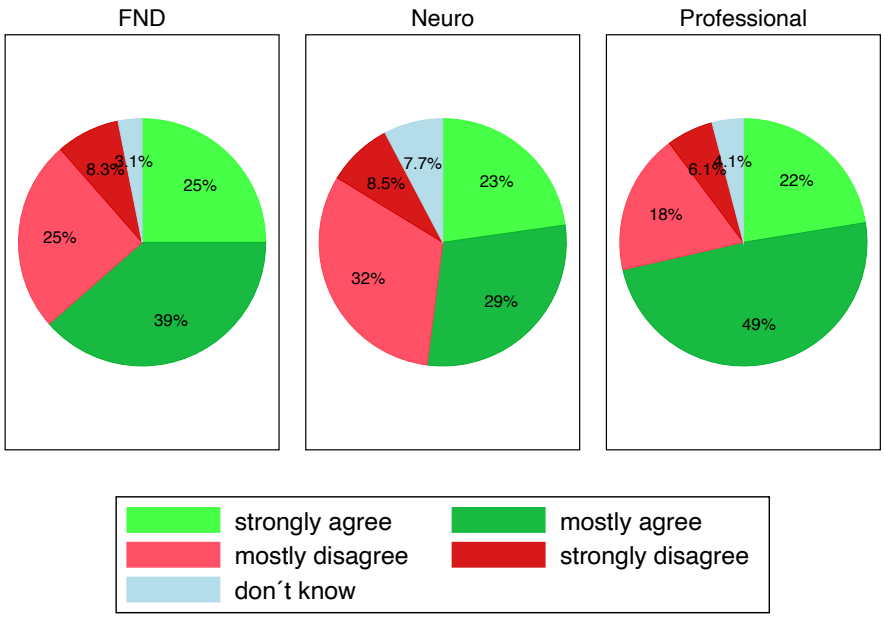


Figure 82: Q3a

Healthcare professionals seemed to worry more that deceptive placebo use would lead to loss of trust in the medical profession, than patients (Table 83). However, this distinction was only statistically significant compared to the neurological patients (Pearson's chi-square $\chi^2(1) = 5.28$, $p = .022$), but not compared to the patients with a functional neurological disorder (Pearson's chi-square $\chi^2(1) = 1.14$, $p = .29$)

	Agree	**Disagree**
FND (n=93)	65.6%%	34.4%
Neuro (n=227)	56.4%	43.6%
Professional (n=47)	74.5%	25.5%
Chi-square goodness of fit	$\chi^2(2) = 6.44$	
	***p* = .040**	

Table 83: Agree versus disagree

b) By receiving deceptive placebo treatments, patients might become over reliant on medicines and interventions, rather than learn to cope and manage their symptoms themselves.

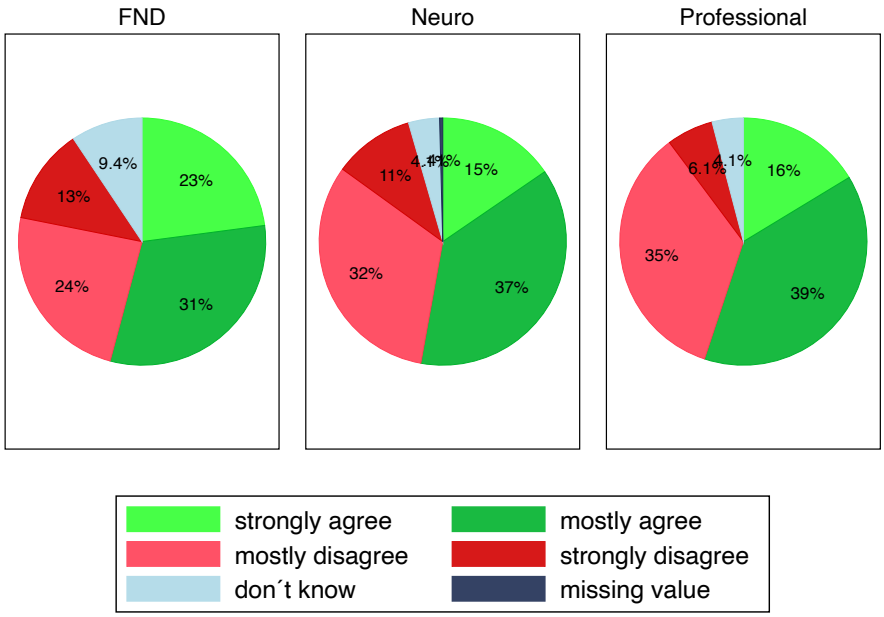


Figure 83: Q3b

The responses of the three groups were similar.

Q4: Placebos work best when the patient does not know that the treatment they are receiving is a placebo (deceptive placebo). However, placebo can also work when the patient is told right from the start that the treatment is a placebo ("open-label placebo").

a) Placebo treatments should only be given in an open way. Patients should be told very clearly from the beginning if a treatment is a placebo, even if that meant it wouldn't work as well.

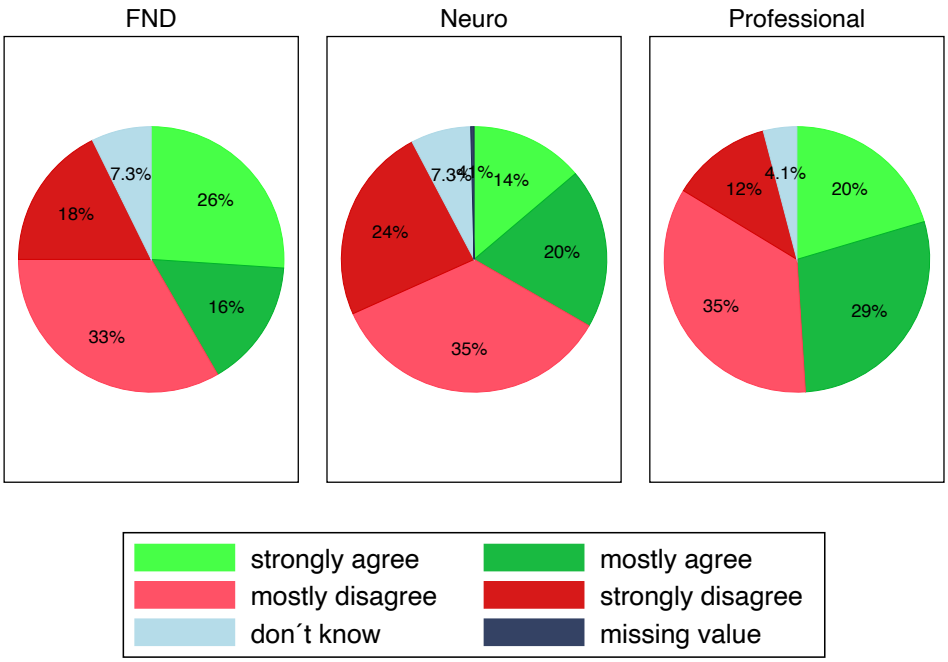


Figure 84: Q4a

The apparent higher disagreement in the neurological patient group did not reach statistical significance (Table 84).

	Agree	**Disagree**
FND (n=89)	44.9%	55.1%
Neuro (n=227)	36.1%	63.9%
Professional (47)	51.1%	48.9%
Chi-square goodness of fit	$\chi^2(2) = 4.71$	
	$p = .095$	

Table 84: Agree versus disagree

b) If a doctor were to give a placebo, they should *not* tell the patient that it is a placebo so that it is as effective as possible, even if that meant the doctor not telling the full truth.

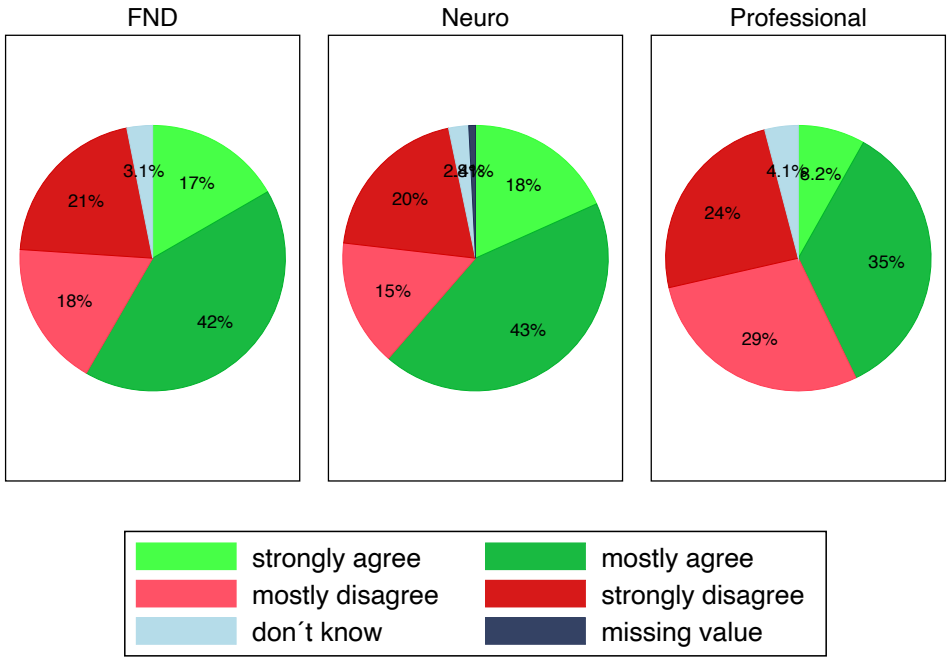


Figure 85: Q4b

There was a trend for the disagreement to vary between the groups (Table 85: Agree versus disagree).

	Agree	**Disagree**
FND (n=93)	60.2%	39.8%
Neuro (n=238)	63.5%	36.6%
Professional (47)	44.7%	55.3%
Chi-square goodness of fit	$\chi^2(2) = 5.77$	
	***p* = .056**	

Table 85: Agree versus disagree

c) It is acceptable for a doctor to give a placebo without telling the patient that it is a placebo and instead to remain vague and say: "This treatment sometimes works really well against the type of problems you have, so let's give it a try."

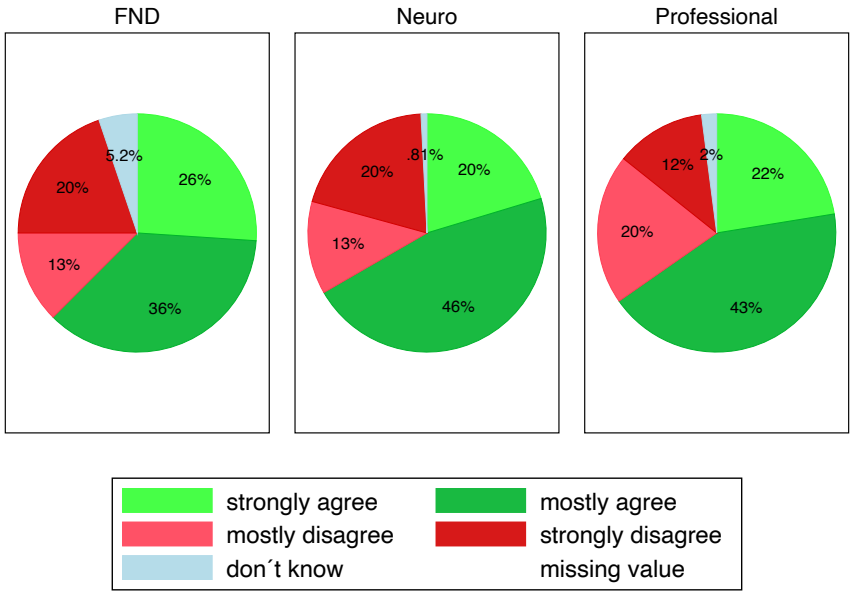


Figure 86: Q4c

d) I think that open label placebo treatments (telling the patient that it is a placebo and that placebos are powerful) work just as well as deceptive placebo treatments (not telling the patient that it is a placebo).

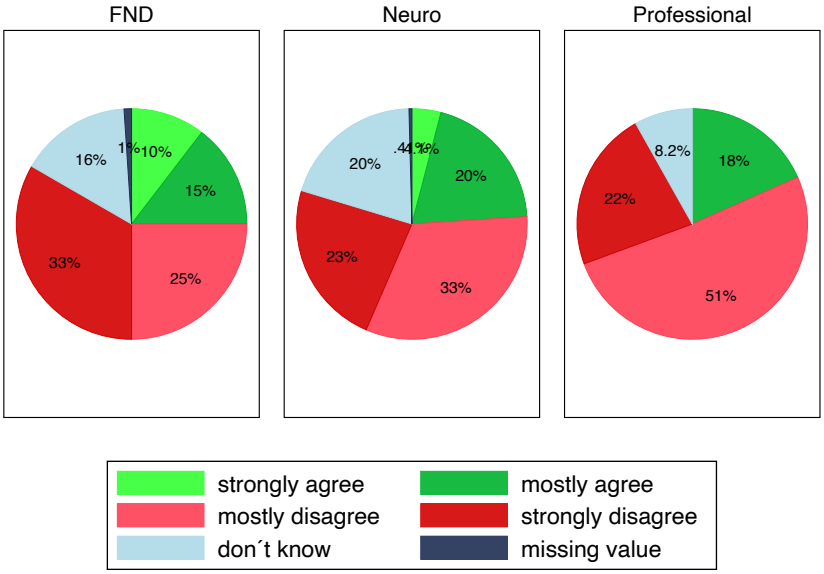


Figure 87: Q4d

The percent of subjects disagreeing was not significantly different between the groups (Table 86).

	Agree	Disagree
FND (n=80)	30%	70%
Neuro (n=196)	30.1%	69.9%
Professional (45)	20%	80%
Chi-square goodness of fit	$\chi^2(2) = 1.92$	
	$p = .38$	

Table 86: Agree versus disagree

e) Imagine your doctor giving you a placebo treatment for a medical problem. When would you want your doctor to tell you that the treatment is a placebo? *Select all that apply*

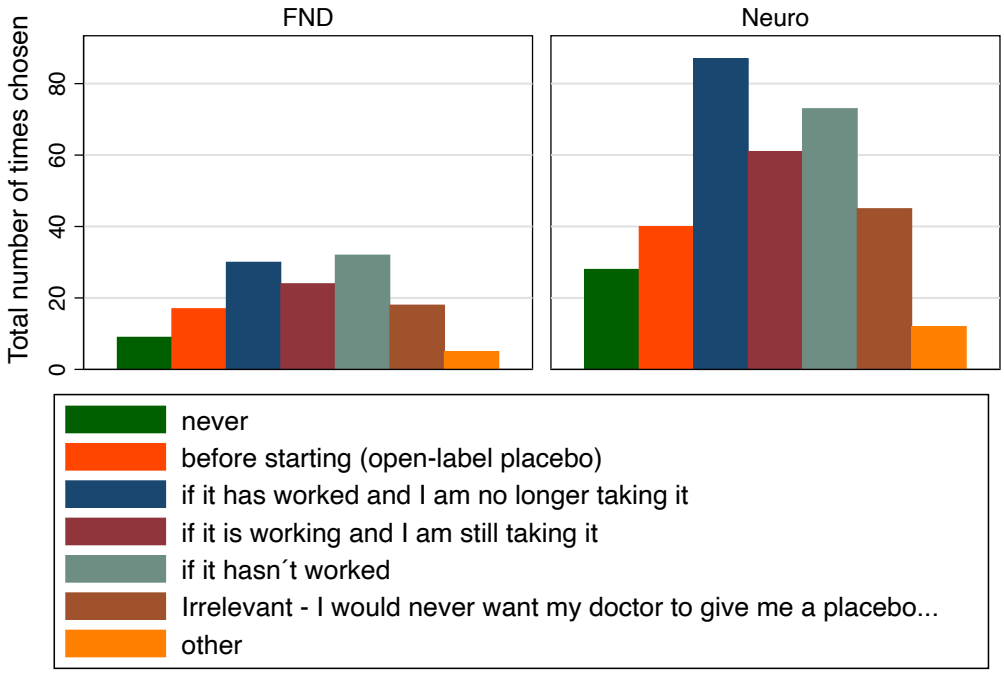


Figure 88: Q4e

The bar graph plots the number of times each specific response was chosen. Patients could choose as many as applied.

Q5: Although nearly any condition can be associated with a placebo effect, only some conditions can show it to an extreme degree. A placebo could therefore be used to help make a diagnosis of these types of conditions. It is acceptable to use a deceptive placebo as a diagnostic tool in such cases.

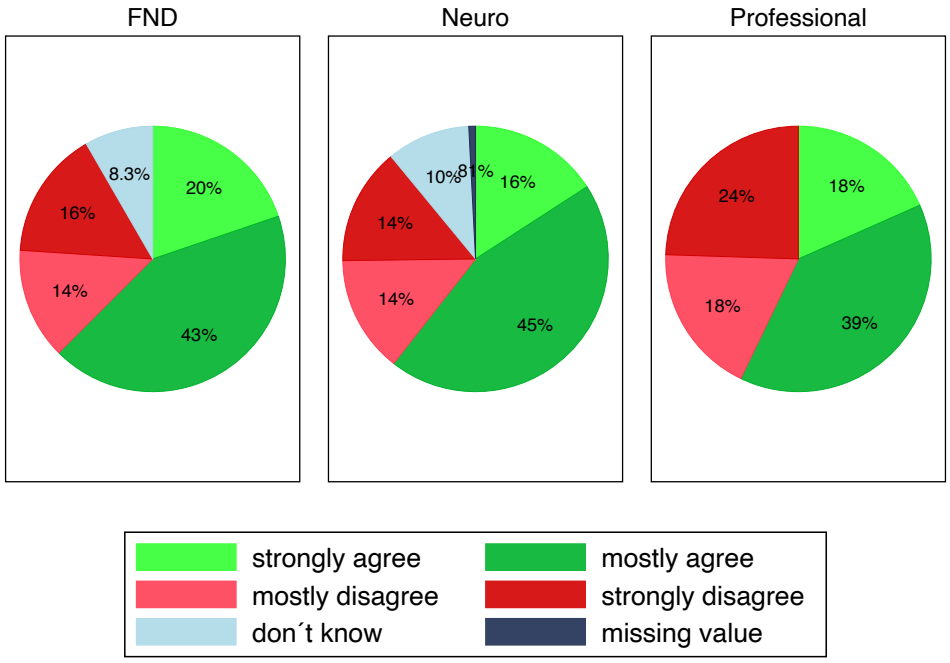


Figure 89: Q5

Q6: Some disabling conditions sometimes show strong placebo responses, with full recovery. In such cases, if standard treatments are unsuccessful, a doctor should attempt the following:

a) *Deceptive* placebo

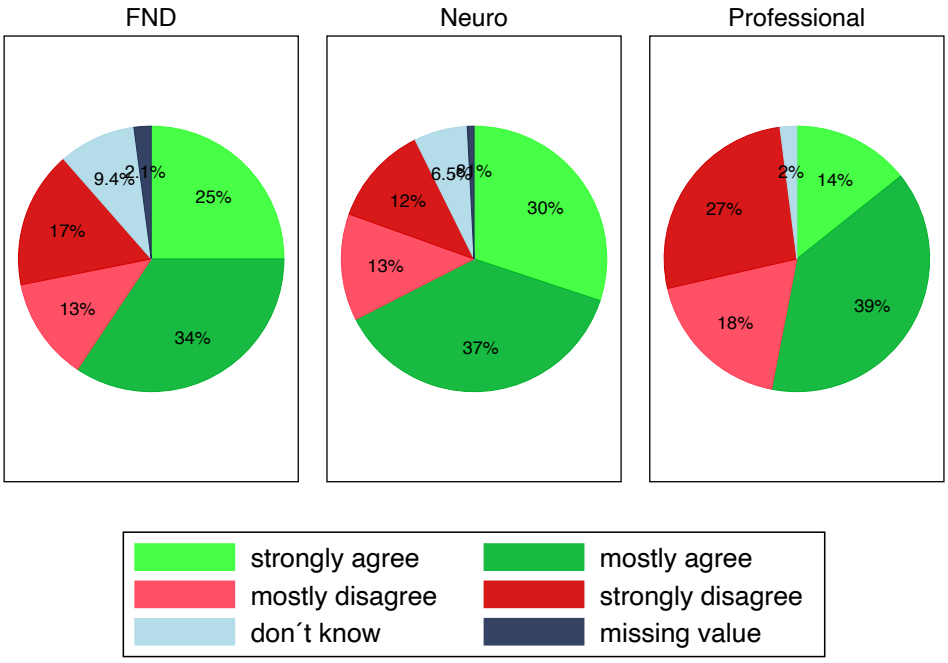


Figure 90: Q6a

b) *Open-label* placebo

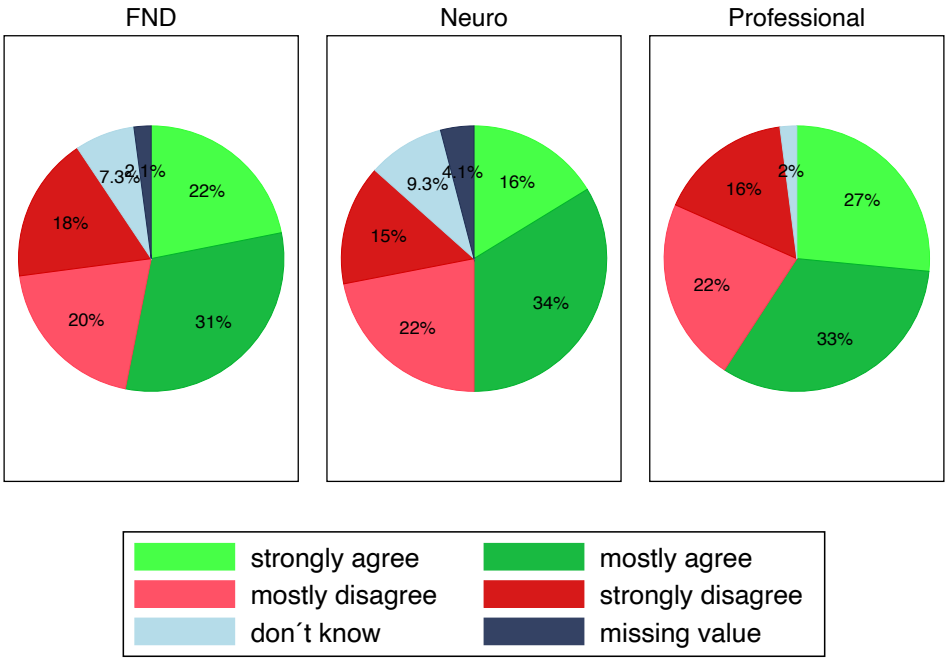


Figure 91: Q6b

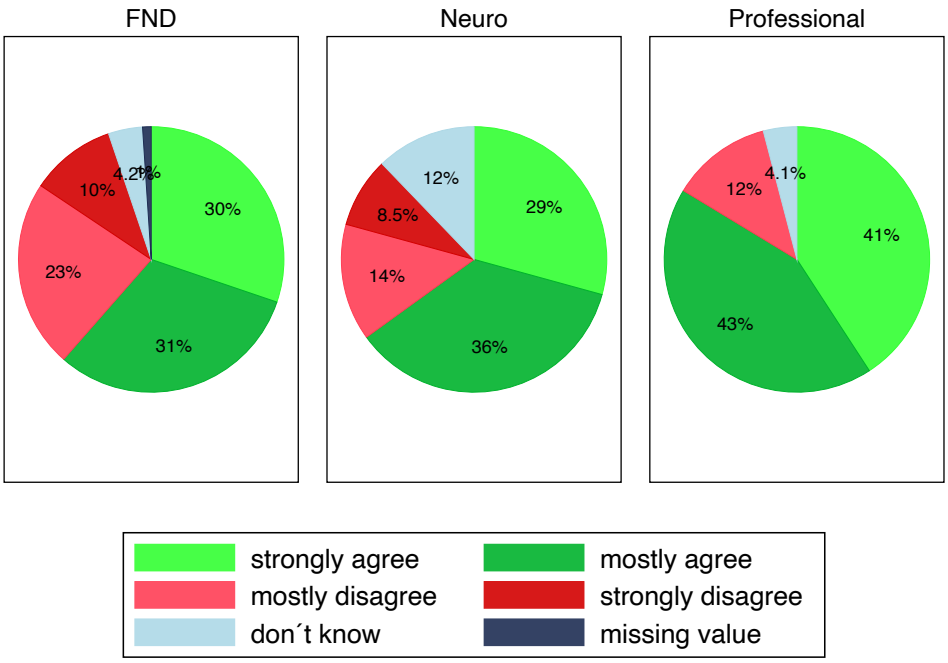
With regards to deceptive placebo use, there was a significant difference in agreement and disagreement between the three groups (Table 87). However, sub-analysis indicated that the healthcare professionals differed significantly only from the neurological patients (Pearson's chi-square $\chi^2(1) = 6.51$, $p = .011$), but not from the FND group (Pearson's chi-square $\chi^2(1) = 2.17$, $p = .14$).

	Agree	**Disagree**
FND (n=85)	67.1%	32.9%
Neuro (n=228)	72.8%	27.2%
Professional (48)	54.2%	45.8%
Chi-square goodness of fit	$\chi^2(2) = 6.63$	
	$p = .036$	

Table 87: Agree versus disagree

With regards to open-label placebo use there was no significant difference between the three groups (Pearson's chi-square $\chi^2(1) = 1.2$, $p = .94$).

Q7: An active (standard) drug will work better if it is given by a doctor the patient trusts fully, than if it is given by a doctor the patient trusts less.



There was a significant difference between the three groups. Sub-analysis confirmed that the healthcare professionals differed significantly from the FND group (Pearson's chi-square $\chi 2(1) = 7.79$, $p = .005$) but there was only is a trend with regards to the difference to the neurological patients (Pearson's chi-square $\chi 2(1) = 3.71$, $p = .054$).

	Agree	**Disagree**
FND (n=91)	64.8%	35.2%
Neuro (n=216)	74.1%	25.9%
Professional (47)	87.2%	12.8%
Chi-square goodness of fit	$\chi^2(2) = 8.08$	
	***p* = .018**	

Table 88: Agree versus disagree

Q8: If a patient fully trusts a doctor, and that doctor tells the patient that their medical problem can improve or disappear if the patient believes it will, then this would work just as well as a placebo treatment.

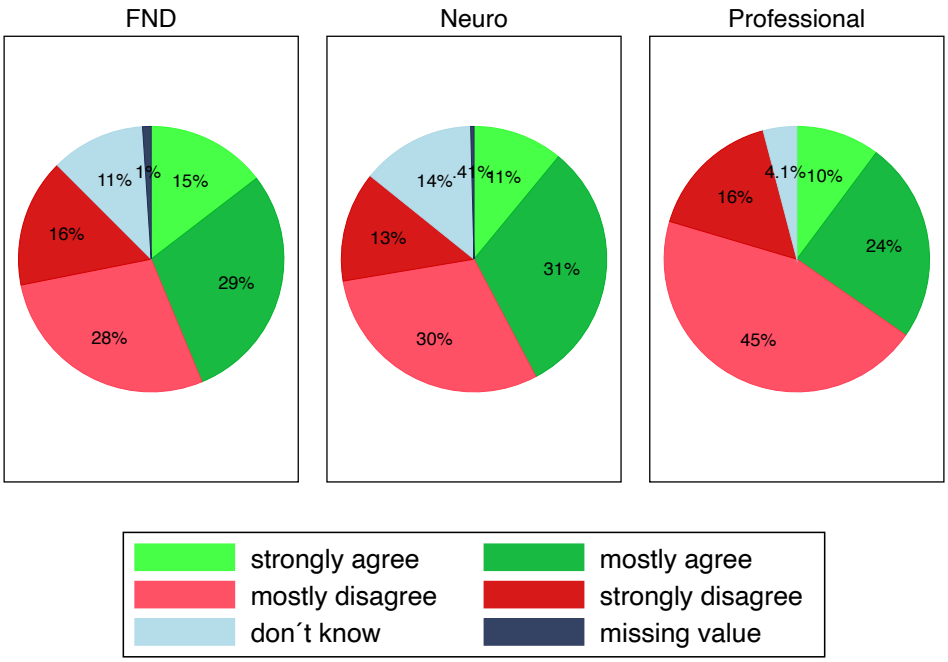


Figure 92: Q8

There was no significant difference between the three groups (Pearson's chi-square $\chi^2(2) = 2.90$, $p = .24$).

Q9: The most important factors for me to fully trust a doctor are

(Please choose 5 from the following)**:**

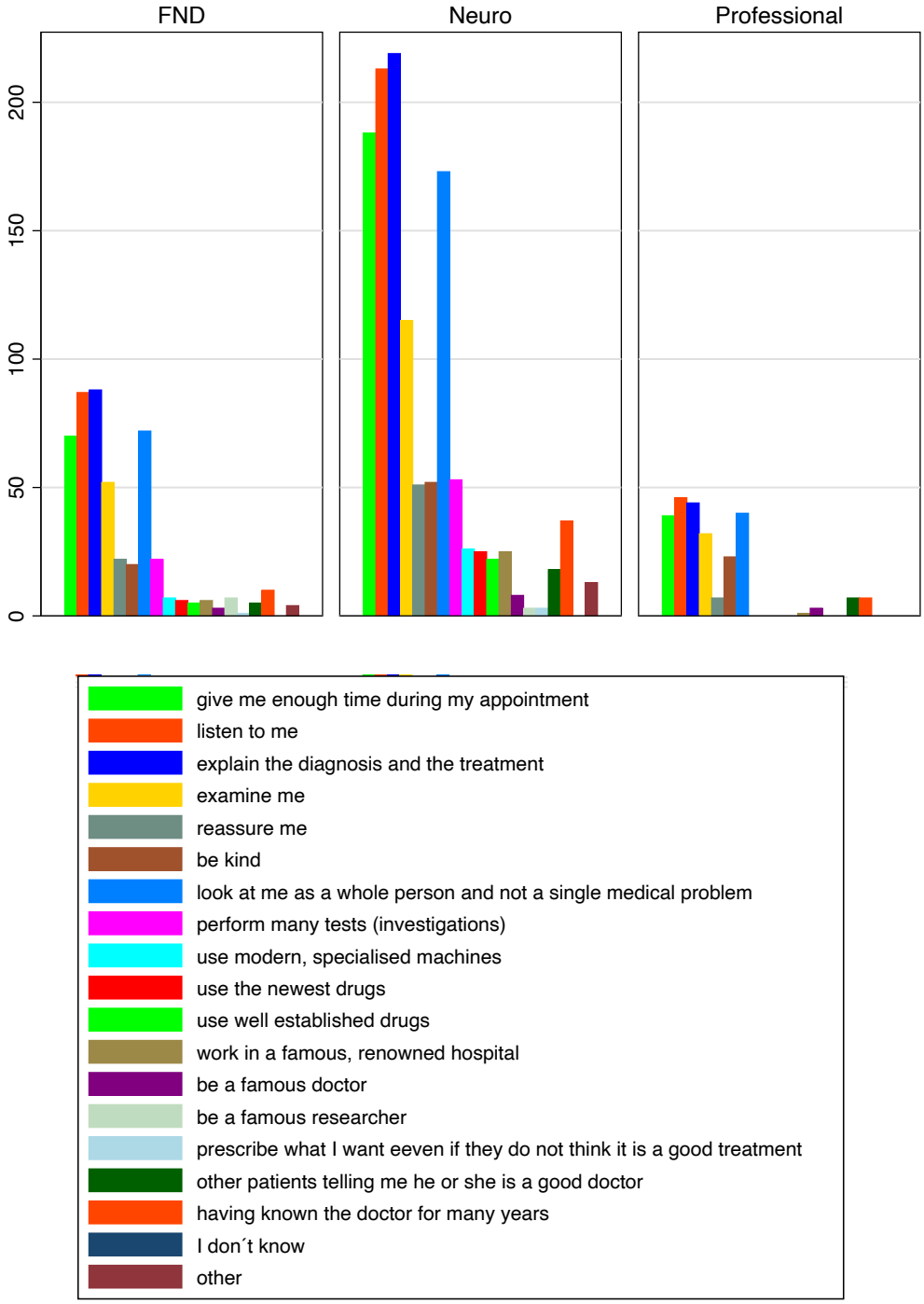


Figure 93: Q9

Q10: A 40-year-old man cannot move his legs and has been wheelchair-bound for 4 years despite many different treatments. All tests are normal and specific features on examination make the doctors diagnose a functional neurological disorder. This type of disorder is real and common. It may improve or persist. The doctor should give him the following:

a) a *deceptive* placebo

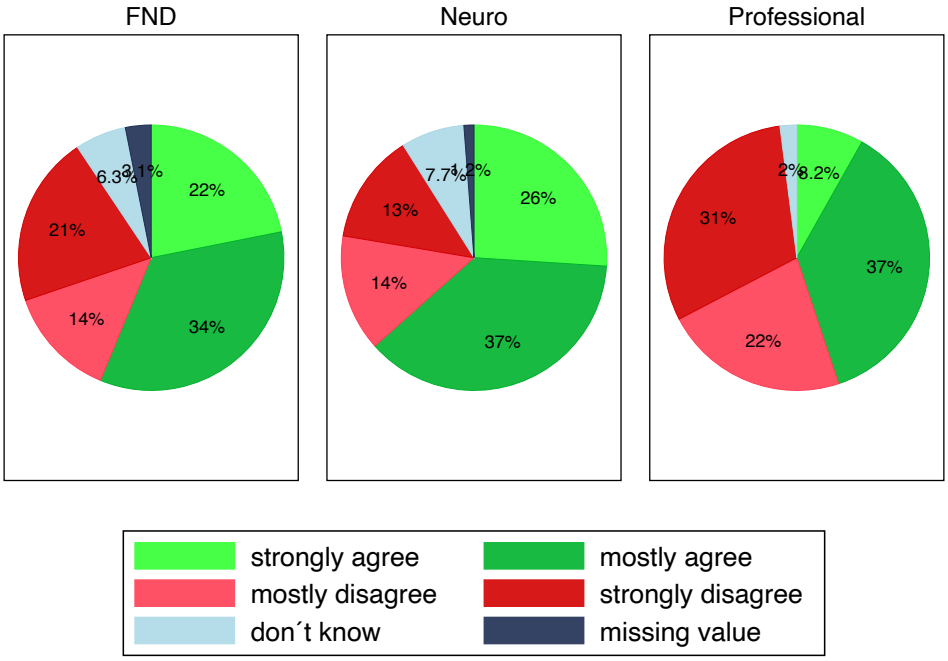


Figure 94: Q10a

b) an *open-label* placebo drug

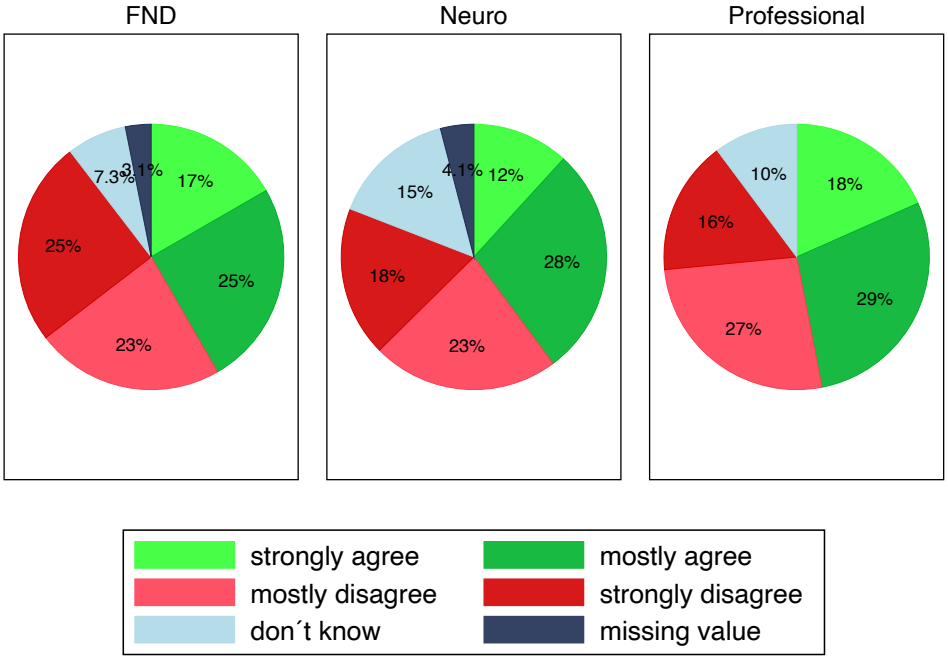


Figure 95: Q10b

With regards to deceptive placebo use, there was a significant difference in agreement and disagreement between the three groups (Table 87). Sub-analysis indicated that the healthcare professionals differed significantly from the neurological patients (Pearson's chi-square $\chi 2(1) = 9.91$, $p = .002$), but there was only a trend in the difference to the FND group (Pearson's chi-square $\chi 2(1) = 3.31$, $p = .069$).

	Agree	**Disagree**
FND (n=87)	62.1%	37.9%
Neuro (n=224)	69.6%	30.4%
Professional (48)	45.8%	54.2%
Chi-square goodness of fit	$\chi^2(2) = 10.13$	
	***p* = .006**	

Table 89: Agree versus disagree

Q11: Now that you have answered some more questions, we would like to ask you the same question as at the beginning. Do you think doctors should use deceptive placebo treatments if they think their patient could get a beneficial placebo effect from it?

(Please don't go back and change your initial answer)

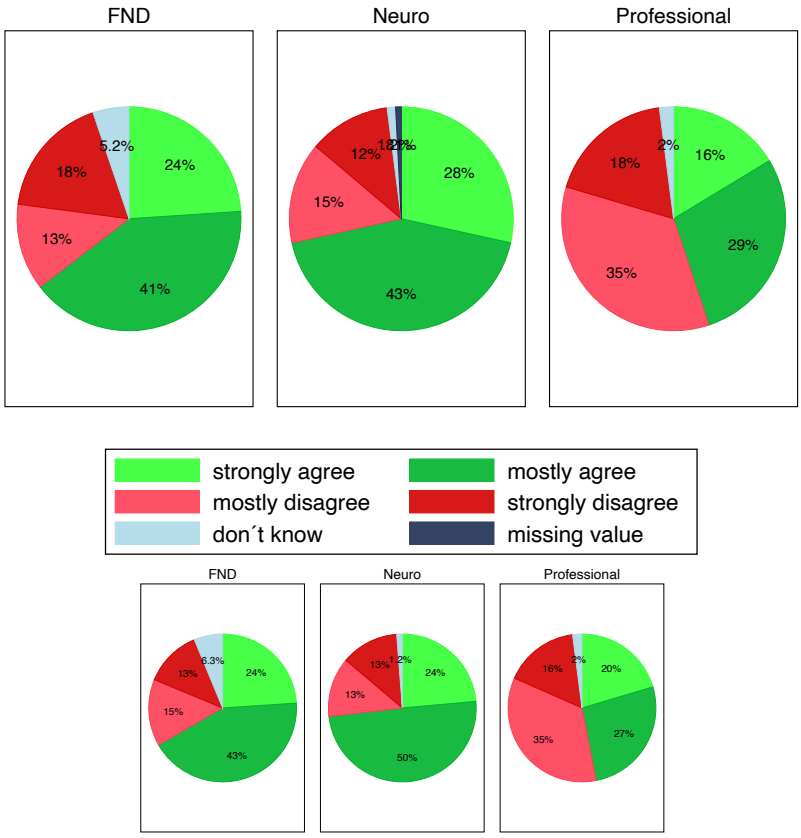


Table 90: Q11 (the initial answer to this question (Q1) is shown for comparison below)

The same question as at the very beginning, whether doctors should use deceptive placebo treatments, was asked again at the end, after different issues surrounding the use of deceptive placebo treatments had been considered. The overall opinion did not change, patients remained rather in favour and healthcare professionals remained almost split, but rather opposed.

	Agree	**Disagree**
FND (n=91)	68.1%	31.9%
Neuro (n=241)	73.0%	27.0%
Professional (48)	45.8%	54.2%
Chi-square goodness of fit	$\chi^2(2) = 13.71$	
	***p* = .001**	

Table 91: Agree versus disagree

Healthcare professionals only:

Q13: Please tick the box corresponding to your approximate use in clinical practice of *open-label*(question a) and *deceptive* placebo (question b):

(Examples of deceptive placebo are:

- telling the patient that it is a specific treatment, when it is in fact just a placebo
- giving a medication which has no effect in that specific condition, other than through a placebo effect
- giving an active treatment at an excessively low dose, so that there is no rationale for it to have any effect other than through a placebo effect

Open label placebo implies giving the patient a treatment, while explicitly telling the patient that the treatment is a placebo, that it contains no active ingredient; or that the active ingredient it contains is useless for their condition and that the effect will therefore be a pure placebo effect. This can be accompanied by positive suggestion, but it is not positive suggestion alone.)

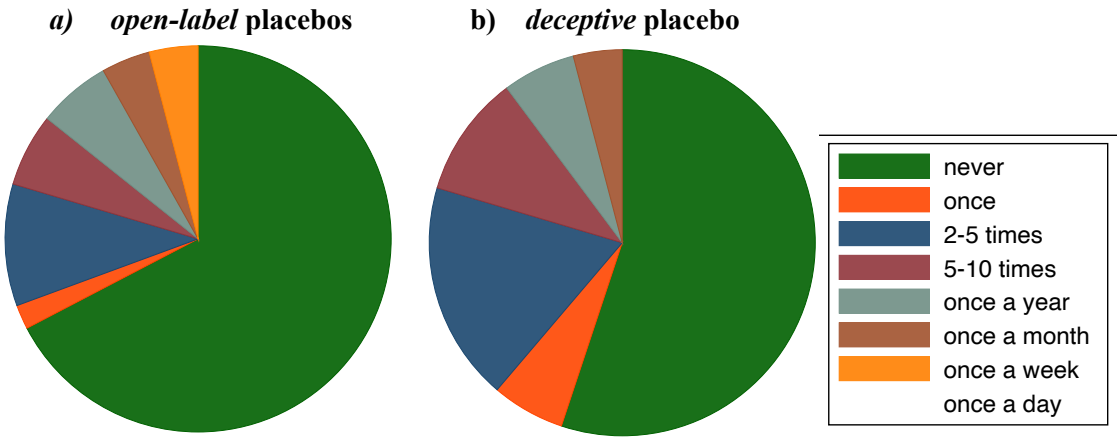


Figure 96: Q13

Healthcare professionals who indicated that they had used open-label placebo treatment at least once were asked the following question:

In which circumstances have you previously used <u>open-label</u> placebo?
(select all that apply)

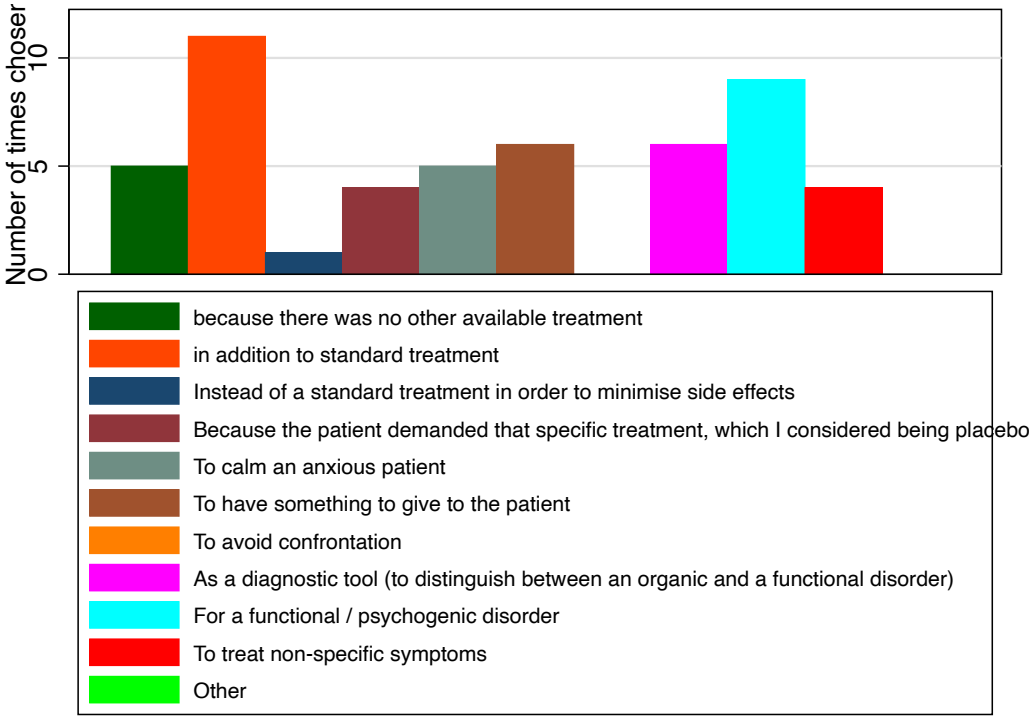


Figure 97: Q13a supplementary question

Healthcare professionals who indicated that they had used deceptive placebo treatment at least once were asked the following two questions:

In which circumstances have you previously used deceptive placebo? (select all that apply)

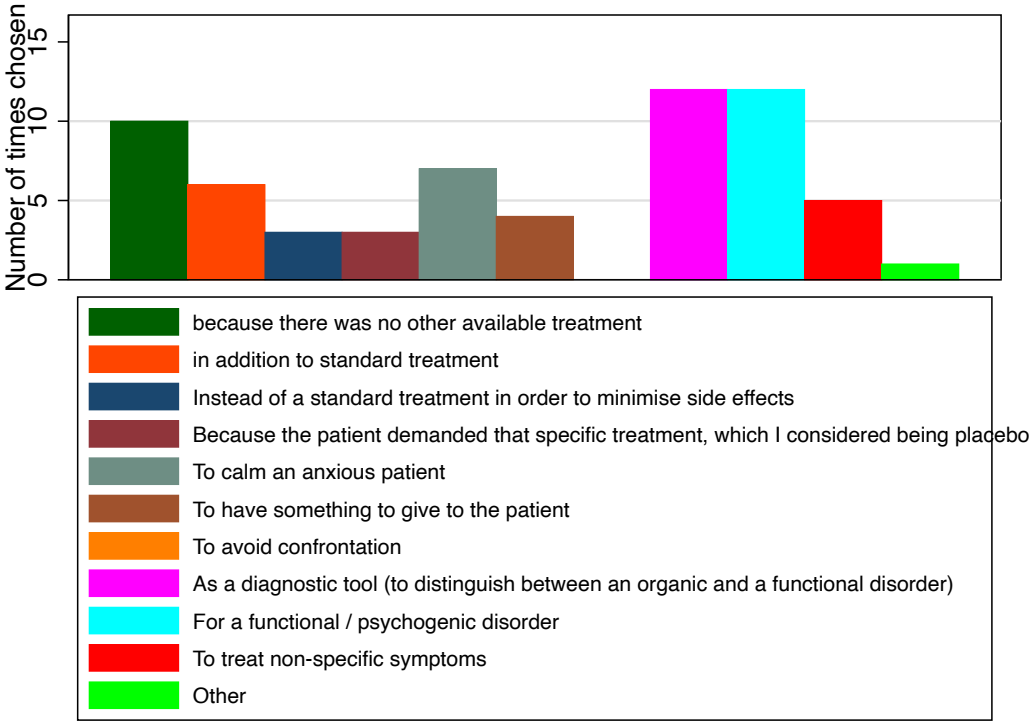


Figure 98: Q13b supplementary question

When you use a deceptive placebo, what do you say to the patient?

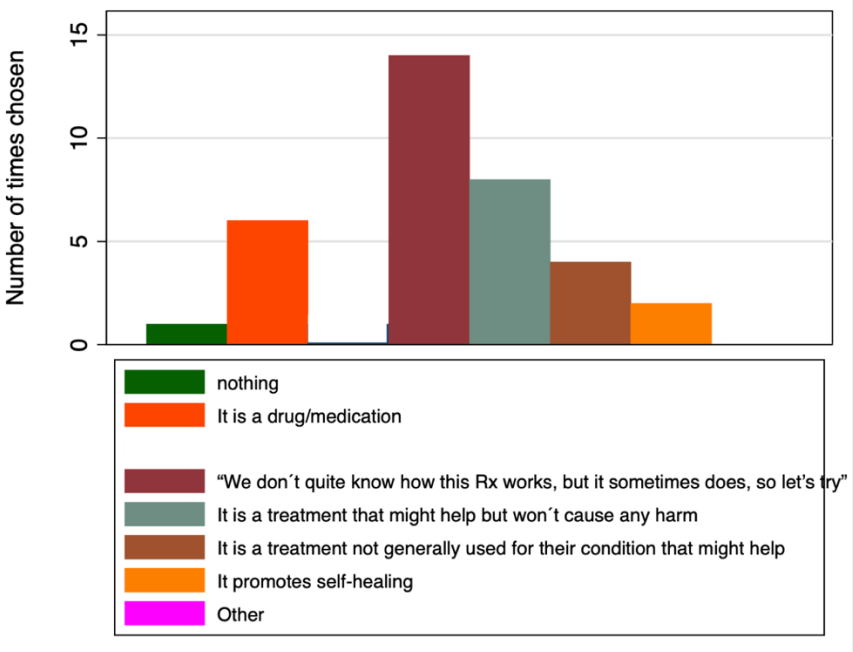


Figure 99: Q13b supplementary question

Healthcare professionals who indicated that they had never used deceptive placebo treatment were asked the following question:

<u>If</u> you were to use deceptive placebo, what would you say to the patient?

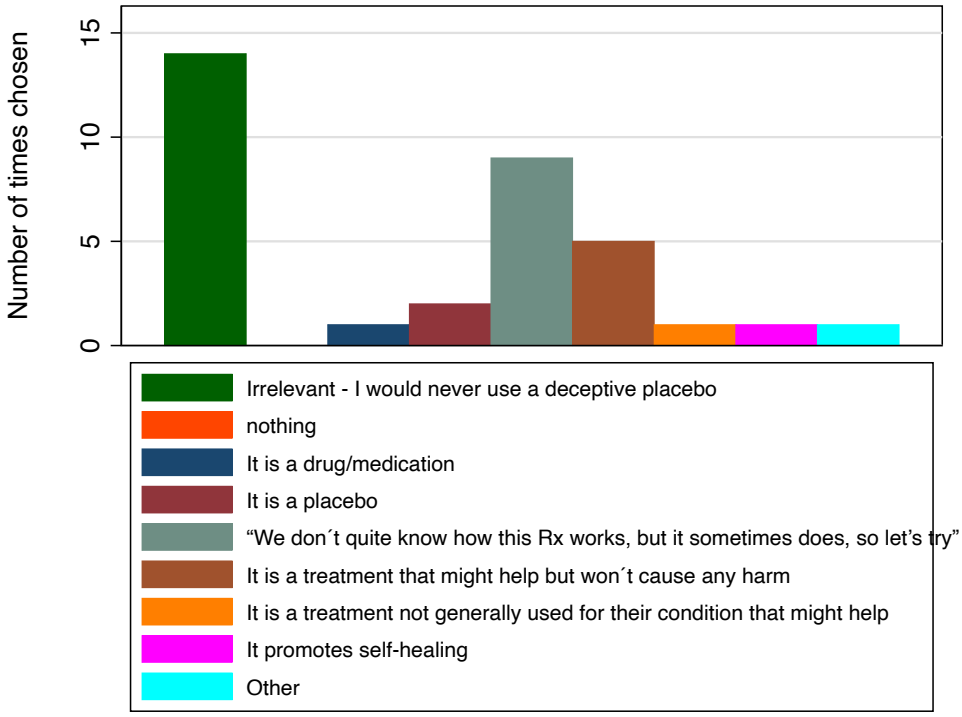
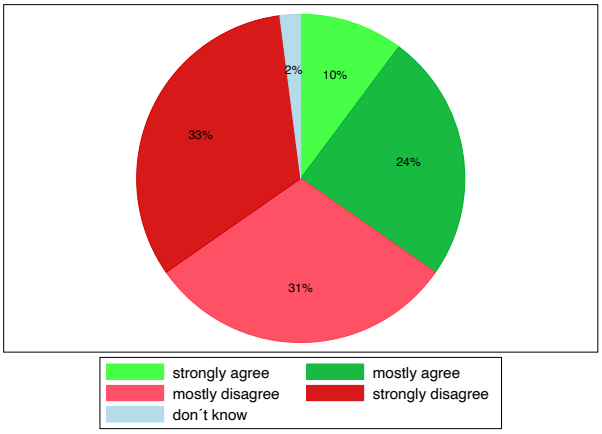


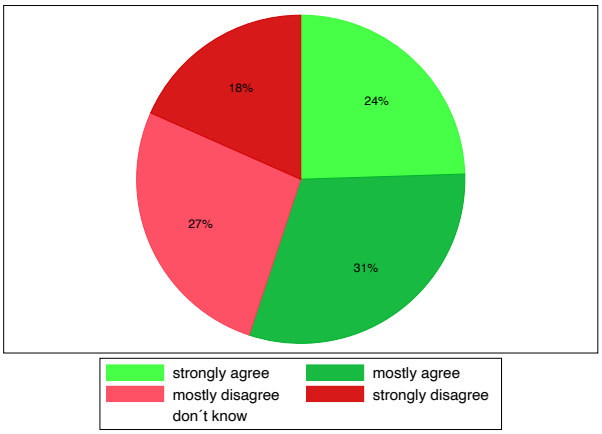
Figure 100: Q13b supplementary question

Q14: Overall, it is ethically acceptable to use deceptive placebo treatments if there are no better treatment options in:

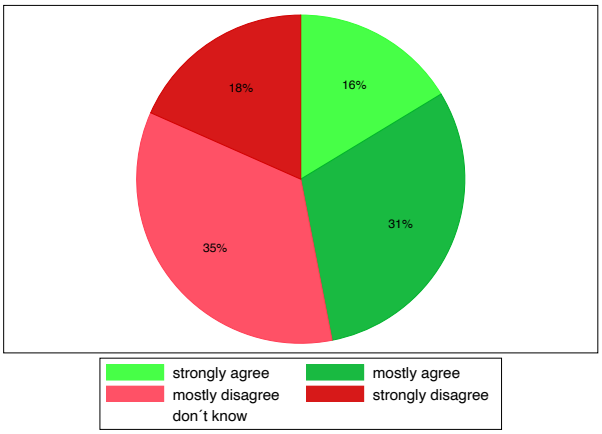
a) Purely organic disorders



b) Purely functional (psychogenic) disorders



c) Mixed organic and functional (psychogenic) disorders



4.3.2.3 Interim discussion

A clear limitation of this survey is the low response rate, which might lead to a bias. On the other hand, it might similarly attract people who are strongly in favour or strongly against, thus balancing each other out. A further limitation is the low participation by healthcare professionals. The survey is still ongoing and will hopefully reach larger numbers.

In summary, healthcare professionals seem to have more conservative views on the use of deceptive placebo treatments than patients, and patients with functional neurological disorders slightly more so than patients with an organic neurological disorder.

Nevertheless, many patients and also healthcare professionals are in favour. This might be partly linked to the fact that many believe placebo treatments to be effective in improving symptoms.

Concerning the potential use of placebo treatments in functional neurological disorders, the first interesting finding to highlight is that the healthcare professionals' estimate for the response rate for organic symptoms was virtually the same as the organic neurological patients' estimate. In the case of functional symptoms, however, the healthcare professionals' estimate was far higher than the patients'. Fifty-five percent of healthcare professionals mostly or strongly agree that it is ethically acceptable to use deceptive placebo treatments if there are no better treatment options for purely functional disorders. This figure decreases to 35% when asked the same question with regards to purely organic symptoms. The question whether functional neurological disorders should be treated with deceptive placebo if standard treatments are unsuccessful, was answered in favour by more than half of all participants, but an essential detail to notice is that not only are 27% of healthcare professionals strongly against it but also 17% of patients with a functional neurological disorder. Similarly, in the clinical vignette of the patient with functional paralysis, 21% of patients with a functional neurological disorder strongly disagree with the use of a deceptive placebo treatment. Sixteen percent of patients with a functional neurological disorder also disagree with the use of a placebo as a diagnostic tool. The most important factor is probably not so much what percentage is in favour, but rather what percentage, particularly of patients, is strongly opposed. If a deceptive placebo treatment was given to a patient who strongly disagrees with this type of intervention, then the consequences can be serious. Even an intermediate option between deceptive and open label placebo, namely to remain vague and say "This treatment sometimes works really well against the type of problems you have, so let's give it a try.", which seems to be the healthcare professionals' preferred option if any deceptive placebo were to be used, is strongly opposed by 20% of patients.

There is some concern that deceptive placebo treatments might hinder patients to learn to cope and manage their symptoms themselves. There is considerable concern about the risk of the use

of deceptive placebo treatments leading to loss of trust in doctors and in the medical profession. The introduction of placebo into clinical practice would probably initially lead to a honeymoon period during which it would be very effective as no patient would suspect it. Over time its use would undermine the trust in the medical profession and patients would begin to doubt that the treatment they are receiving is an active medication. This would not only diminish the placebo effect but also lead to a lessebo effect (the decrease in efficacy of an active treatment because the patients think they might be receiving a placebo). It is well known, that the more extreme or expensive the apparent treatment, the stronger the placebo response (de Craen et al. 2000; Espay et al. 2015). This could quickly lead to a slippery slope with more and more drastic and risky treatments or interventions being used as placebo treatments; deep brain stimulation for functional disorders being one extreme example. Symptom recurrence, which frequently occurs with placebo treatments, might lead to a dependence on placebo treatments or an escalation with more and more risky placebos, leading into a spiral of deception and the potential of iatrogenic harm.

The use of deceptive or open-label placebos is low in this group of healthcare professionals. The fact that almost half report having used it at least once might, however, raise concern in view of the fact that the use of deceptive placebo is prohibited in the UK. Some of this use might have occurred in healthcare systems in which its use is legal. The other possibility is that the deceptive placebo was an impure placebo. This term is ill defined and generally unhelpful, which is why it was not included in this survey. A “pure” placebo is a substance that is never used as a treatment. An impure placebo is a therapeutic substance used either at a very low and thus ineffective dose, or a substance used for a completely different condition, in which it is not presumed to have any effect. The distinction “pure” vs “impure” is artificial, as even sugar, saline or water are treatments for certain symptoms, and thus impure placebos. An impure placebo is effectively the same as a pure placebo, except that it is used as a real treatment in other conditions. All this said, impure placebos span a wide grey zone, in which there is the possibility of pretending that the treatment was given for a different reason, even though the real intention was the induction of a placebo effect. The use of botulinum toxin in functional dystonia is one such example.

Overall placebo effects are very powerful and could benefit patients, yet deceptive placebo is associated with risks that do not seem to be worth taking. It might be worthwhile, taking a step back and thinking about what the factors are that contribute to a placebo effect. Surely, a street vending machine administered placebo in response to four answered questions would not lead to a significant placebo response.

Core elements in a placebo effect are previous experience and the belief in the improvement of symptoms. Many factors both at an individual and at a societal level contribute to the formation of this belief: trust in the medical profession, in science, in medical treatments, in specific

institutions or individuals; previous personal or observed positive experience; the learned association or indeed conditioned response from a young age of symptom improvement in response to a medical visit or treatment; and reassurance when being cared for by a healthcare professional with a resulting decrease in anxiety and rumination. Indeed, this questionnaire suggests that some of the most important factors for a patient to gain trust in their doctor are for the doctor to explain the diagnosis, to listen to their patient, to give them enough time during the consultation, to look at the person as a whole and not as a single medical problem and to examine the patient. Furthermore, this survey found that 84% of healthcare professionals agreed that a standard medication would work better if it was given by a doctor the patient trusts. More than 60% of patients also agreed with this statement. However, most healthcare professionals did not believe that a doctor's positive suggestion and reassurance could be as effective as a placebo treatment. The patients were evenly split between agreeing and disagreeing on this point.

The placebo effect, be it in response to a placebo treatment or the enhancement of an active treatment is a reflection of all the factors discussed above, it would not exist without them. Benedetti nicely summarises it: "Indeed, a placebo is the whole ritual of the therapeutic act."(Benedetti 2014)

Being deceived as to the nature of the treatment, is a quick and easy way of leading to the placebo effect as it uses the beliefs and trusts already established for treatments. However, deception is not an essential component of a placebo response. Hence the question, whether open-label placebo could be an option. Judging from this survey, there does not seem to be much enthusiasm for open-label placebo, neither from patients nor from healthcare professionals. It is largely not believed to be effective, or at least not as effective as deceptive placebo.

However, several studies suggest that open-label placebo administration is as effective as and possibly even more effective than deceptive placebo (Carvalho et al. 2016; Charlesworth et al. 2017; Kaptchuk et al. 2010). The essential factors seem to be a convincing explanation of the power of placebo, coupled with strong positive suggestion.

One could view open label placebo as the willingness to change one´s beliefs in the context of positive suggestions, with the addition of the ritual of a treatment, e.g. the daily ingestion of a placebo pill. The latter utilises the pre-existing conditioned response to treatments, thus acting symbiotically with the willingness to change the belief. At its core, a placebo is a way of changing unhelpful beliefs and utilising positive suggestions. There are ways of achieving this without any placebo or placebo effect or indeed any associated medication. However, in select patients who are open to the idea of an open-label placebo, this type of intervention might be very powerful, both in terms of symptom improvement and self-management.

Chapter 5 General discussion

5.1 Key findings

Each experiment has been discussed previously. As an overview, the main findings the data suggest are briefly summarised.

Chapter 1 - Attention:

- The executive network is abnormal in functional neurological disorder patients compared to healthy controls and organic neurological controls. The other aspects of attention, the alerting and orienting networks are unaffected.
- In functional tremor, attention seems to be misdirected on the ongoing visual feedback of the movement. This misdirected attentional focus seems to partly contribute to symptom generation, or at least aggravate the symptoms, since attention to the visual feedback of the movement, in particular in terms of its quality, impairs movement performance in patients with an organic tremor and in healthy controls. Focusing on the immediate target improves functional tremor to some degree. Finally, functional tremor is improved when the patients' attention is focused on something occurring entirely after the movement, or when the movement is believed to be of no importance.
- Patients suffering from a movement disorder, report a higher tendency to consciously monitor their movement, regardless of whether the movement is of functional or organic nature. It can be presumed to be the consequence of having a movement disorder that leads to patients being more conscious and mindful of their movement.

Chapter 2 - Agency:

- Subliminal priming leads to normal reaction times in patients with functional movement disorders, confirming, that the implicit motor system functions normally.
- The current study did not find any abnormalities of the explicitly reported sense of agency in functional neurological patients compared to healthy controls with subliminal nor with supraliminal priming. As already discussed, the sense of agency is difficult to study and it remains uncertain, whether agency really is unaffected or whether the applied methods did not allow its appropriate measurement.

Chapter 3 - Beliefs:

- Functional tremor patients´ perception of their own tremor is accurate and not exaggerated.
- Transitorily modifying the visual feedback of their movement in an attempt to change their beliefs, does not have any measurable effect on subsequent tremor.

- Patients with functional neurological disorders are not more susceptible to placebo analgesia than healthy controls. Furthermore, they seem to underreport pain intensity compared to healthy controls.
- Concerning the use of deceptive placebo treatments in clinical practice, healthcare professionals are slightly more conservative than patients. However, a non-negligible proportion of patients, particularly patients with a functional neurological disorder, are strongly opposed to the use of deceptive placebo. There seems to be overall scepticism with regards to the use of open-label placebo.

5.2 Model of symptom generation & reinforcement

How can these findings be incorporated into a larger model of symptom generation and reinforcement and how can they be used to guide therapy?

Predisposing factors

As discussed in 1.1, minor physical injury or illness frequently seems to trigger the onset of functional movement disorders (Pareés et al. 2014; Stone et al. 2009). Imagine someone falling over and hurting their wrist. The immediate reaction is to immobilise the wrist. One might even adopt a slightly dystonic posture. When the next movement is attempted, it causes pain. Out of fear of causing further damage or pain, the movements are performed cautiously, slowly, while looking at the wrist and under explicit control so as to proceed very slowly and be able to interrupt the action at any time in case of pain. If this pattern persists over an extended period, it may become entrenched.

The study's results suggest that functional tremor patients´ attention is misdirected onto the visual feedback and that such an attentional focus has a negative impact on movement performance. Attention to visual feedback encompasses many aspects. If paying attention to the visual feedback could not lead to any interference in the ongoing movement, then it probably would not be detrimental. Every parent will know how difficult it is to watch without interfering, particularly when something is going wrong that could be rectified. The reason why attention to the visual feedback has a negative impact on the quality of the movement is likely to be because it leads to interference in the movement, interrupting its implicit execution and replacing it by explicit control. Particularly when the movement is abnormal, interference is likely.

Why does explicit control of the movement lead to impaired performance? Our motor system has evolved to function without conscious control. Or rather, the motor system developed long before consciousness as movements in simple organisms highlight. If we had to control every single movement in a conscious manner, there would be little resources left to do anything else. When learning a new skill, conscious control is required, but once the skill is mastered, the motor system executes it implicitly, freeing up our limited resources for other undertakings. We often forget the complexity of even the most simple of movements. Observing the motor evolution of a child tells us that our motor system has learned and refined its skills over many years. We are in fact not able to move well in a conscious manner, we do not know how much force to apply across which joints at what time in order to perform smooth, accurate movements. Thus, when we attempt it, the result is worse than when we let the motor system perform it implicitly.

Thus, focusing on the visual feedback of the ongoing movement, and interfering in it, in an attempt to improve it by explicitly controlling it, in fact interrupts its implicit execution and culminates in an ill performed movement.

When actions do not turn out the way we intended them to be, we feel a lack of control over them. As a consequence of the bad performance, the sense of control over the movement decreases. The present study could not find any general abnormality in the sense of agency which could have led to further aggravation.

In an attempt to improve the movement and the perceived control over it, a person will try even harder to consciously control the movement and keep checking by means of the visual feedback. This impairs the movement further and the vicious circle is complete.

The findings of this study suggest that the presence of a movement disorder leads patients to consciously monitor their movements. In patients with functional movement disorders, this will exacerbate existing functional symptoms. In patients with organic movement disorders, this tendency might make them more susceptible to developing functional disorders. It might thereby explain, why functional overlay (the presence of functional symptoms in a patient with a pre-existing organic disorder) is relatively common (Onofrj et al. 2011; Parees et al. 2013).

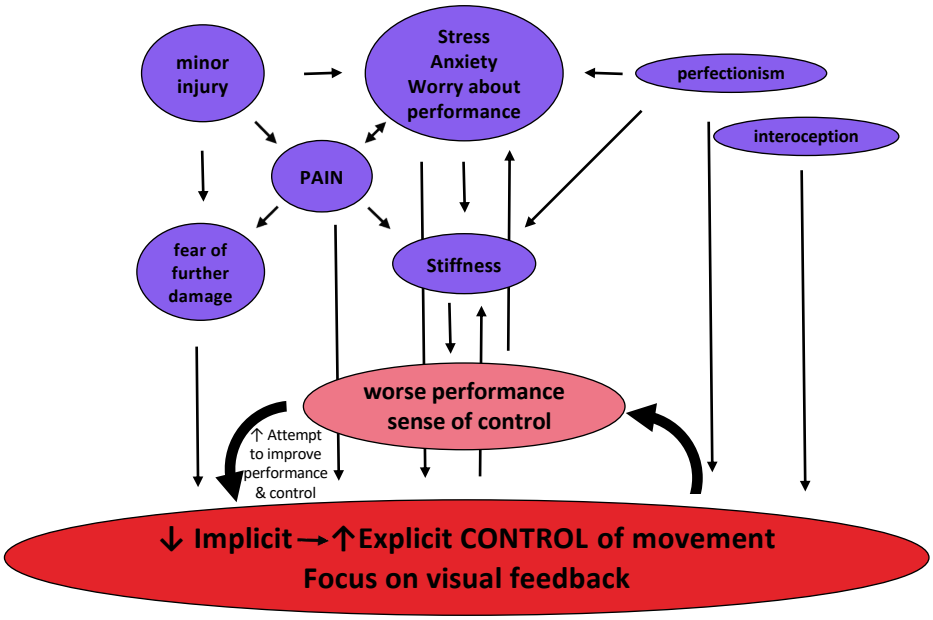


Figure 101: Model of symptom generation and reinforcement in FMD
Predisposing factors are highlighted in purple.

The normal reaction times in the subliminal priming experiment and their normal modulation with the primes confirm that the implicit motor system is functioning normally in patients with functional movement disorders.

Pain can also lead to stress, anxiety and worry about the performance of the movement. Anxiety in return exacerbates pain. Both pain and anxiety cause stiffness, which prevents a fluid movement and impairs its performance. Co-contraction can also directly lead to a tremor.

Pain is by no means an obligatory factor. Anxiety or worry increase the focus on the visual feedback, so as to seek reassurance. In addition, stress or anxiety do not allow the movement to occur implicitly, unchecked, but instead favour explicit control, again in a mistaken attempt to improve the movement. Anxiety could also directly increase the patients' perception of their symptoms, by exaggerating their importance. However, the study´s findings of accurate perception of their tremor and of the lack of overreporting but rather slight underreporting of pain, suggests that the symptoms are not being exacerbated to an abnormal degree in functional neurological disorders.

A previous study found lower rates of conscientiousness in patients with non-epileptic attack disorders than in patients with functional movement disorders, and no difference between patients with a functional movement disorder and healthy controls (Ekanayake et al. 2017). Thus, perfectionism does not seem to be increased in FND. Nevertheless, in patients who do have this personality trait, it is easy to see how perfectionism, would reinforce checking the visual feedback of the movement, prevent its implicit execution and instead favour a more explicit controlled way of moving. Marked interoception would have similar effects.

Consequences

In addition to the impaired movement, several further features of functional neurological disorders might be explained as a consequence of this pattern of movement (Figure 102). Explicitly controlled movements are much slower than implicitly executed movements, thus it might explain the commonly observed slowness of movement.

If movements are not executed automatically, but under explicit control, then they will interact with other voluntary movements, possibly explaining another characteristic feature or functional movement disorders.

The vast majority of movements made throughout the day are done implicitly. Having to use attentional resources for even the simplest of movements places huge demands on the attentional system, effectively hijacking it. This may explain why patients struggle with multitasking, why their executive attentional system is impaired as discussed in 2.1.2.4, why their movements appear effortful and indeed are perceived as such, and ultimately why fatigue is such a common symptom in functional movement disorders.

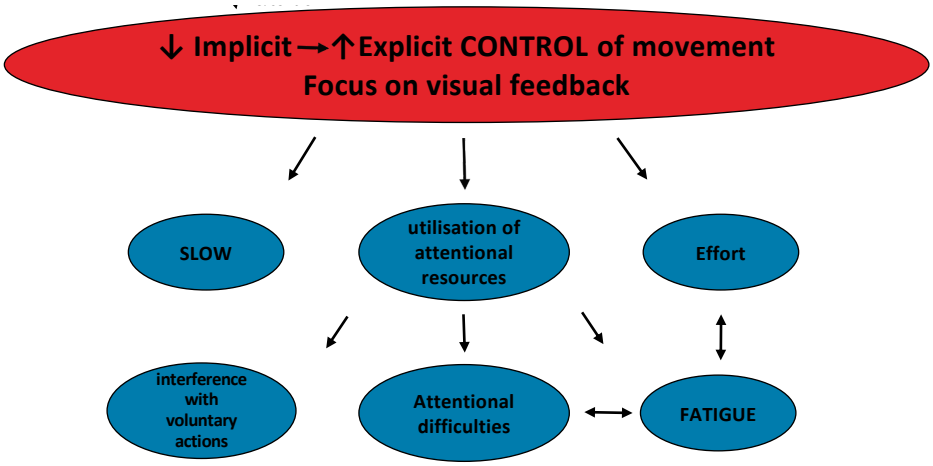


Figure 102: Consequences of increased explicit control of movement

The finding of executive dysfunction seems to be a consequence of the functional neurological disorder, rather than a predisposing factor. However, the way to answer this question is by performing the attention network test in a group of recovered patients, or preferably in the same patients in the symptomatic stage and after recovery.

5.3 Therapeutic implications

The suggested model also highlights where targeted treatments could help break this vicious circle.

It is difficult for attention not to be drawn to pain. The evolutionary function of pain is for attention to be drawn to it so as to eliminate the cause and prevent further damage. Whenever possible, it is important to address any underlying pain as it will make other treatment approaches, such as distraction techniques, less successful. If there is an underlying organic or mechanical cause for the pain, it needs to be treated. If the pain is of functional origin, its treatment is more difficult. Functional pain responds poorly to analgesic medication and a more wholistic approach is required. Pain generally signals damage or danger to the body. Thus, it often helps to address underlying fears of existing, or potential irreversible damage if the limb is being used and to offer reassurance. Underlying depression or anxiety generally worsen pain and need to be addressed.

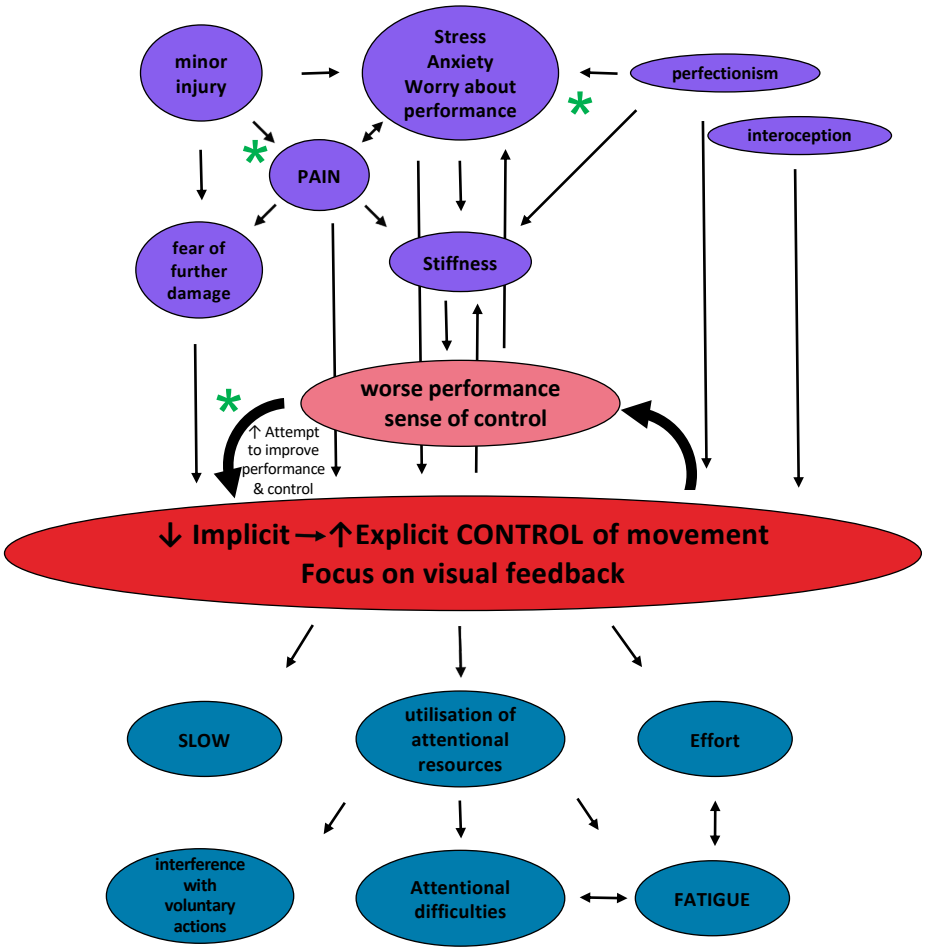


Figure 103: Model of symptom generation and reinforcement in FMD and its consequences
Predisposing factors are highlighted in purple, consequences in blue. The green asterisks indicate where treatments could intervene.

Anxiety, uncertainty, worry and rumination can be a strong driving factor for symptom worsening. In addition to worsening of pain, it is inevitable that worry and uncertainty about symptoms, will lead to increased focus on the symptom, which by itself will heighten its perception and ultimately exacerbate it. The diagnosis of functional neurological disorders can be difficult to understand, and it is easily misunderstood by patients. Clarifying the reasons for the diagnosis will give patients trust in the diagnosis and every possible effort should be made to explain the diagnosis in a non-judgmental, open way.

In more severe cases, or if there is pre-existing psychopathology or trauma, specialised psychotherapy, sometimes in conjunction with medication is indicated.

If present, psychotherapy can also address perfectionist traits, which can contribute to symptom generation and reinforcement.

Cognitive behavioural therapy or similar approaches may be beneficial in virtually all cases since they can address the maladaptive thoughts and behaviours that frequently emerge. Further examples to the ones discussed below, are self-blame or feelings of guilt, frustration and anger and its resulting effects.

Getting the movement to occur in an implicit, automatic manner leads to a well performed movement and can thus break the vicious circle of impaired movement and shift the balance back to implicit rather than explicit movement control. Thus, specialised physiotherapy is often the mainstay of treatment. The special focus is to let the automatic motor processes execute the movement without any type of interference. The more attention-free, the better. Patients are generally told to ignore their abnormal movements in order to improve them. This is entirely correct and is the perfect solution in theory. However, in practice it is very difficult to implement. If a patient´s movement is impaired, it is natural for their attention to be drawn to it. Attempting not to pay attention bears similarities to the notorious “Do not think of a pink elephant”.

What are possible strategies that can help patients shift their attentional focus away from their movement and its visual feedback?

An early key factor is to help patients with functional movement disorders realise that their movements are normal when they are executed in an automatic, implicit way. Video recordings can be very helpful in this context. Knowing that their motor system is able to function normally will help patients regain trust in their movements and pave the way for them to be allowed to occur without any control or interference. Otherwise, if patients cannot trust their movements, they will inevitably keep checking their movements by looking at them, which will ultimately lead to all the consequences referred to above.

The next step is for patients to understand that consciously trying to control their movements is detrimental. It can be explained in generic terms, giving the examples of sports, singing, or walking – if we were to try to consciously control each component of our gait, we would most likely fall over, because we do not consciously know how to walk. The last thing we would probably think of in the process is to hold our trunk upright. Since people do not know how to move, but their motor system does, the motor system should be allowed to do its job without any interference. Trying hard to make the movement perfect or even normal, in fact impairs movement even in healthy subjects, so this should not be attempted. The particular relevance of all of this in functional movement disorders should be stressed.

By this stage patients might understand that their motor system can make their body move normally if it is allowed to do it in an automatic manner. However, how can the natural tendency to interfere be overcome?

It is counterproductive to focus on the movement or its visual feedback, because doing so will make it very difficult, not to interfere. Therefore, one important advice is not to look at their affected limb while moving.

The study showed that moving very slowly leads to impairment not only in functional tremor patients but also in patients with an organic tremor and in healthy controls. Moving quickly, on the other hand, leads to straighter trajectories. Performing a movement unnaturally slowly implicates explicit control as it is needed to slow the movement down. In addition, a slow movement provides ample time for interference. If a movement is performed relatively quickly, there is no time for interference. There is of course a balance between speed and accuracy, but consciously moving slowly is not a good strategy to adopt. Instead the movement should be executed relatively quickly.

Finally, how can patients, who are naturally drawn to paying attention to their abnormal movement, distract their attention away from the movement and its visual feedback so as not to interfere in it and allow it to happen automatically?

Entirely ignoring the abnormal movement and focusing on something that is entirely unrelated to the movement or the task is difficult. Thus, a more natural and hence practical advice is not to concentrate on the ongoing movement, but on what to do next or on the ultimate goal of the movement. Indeed, when patients with a functional tremor performed a reaching movement, thinking it was just an irrelevant preparatory movement before the actual task, they're tremor was less marked than when they performed the exact same movement thinking that it was of some importance. The ultimate goal the attention is to be focused on should be clearly separate from the intermediate goal or target, otherwise it might still be too closely related to the movement.

The example of eating has already been given. Another example is writing a card: the person with a functional tremor should not think of the straightness of the individually formed letters or words but instead of the meaning of the sentence, of what to write next or of the person they card is addressed to.

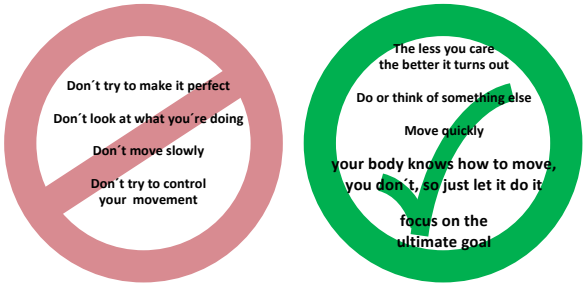


Figure 104: Summary of does and don'ts in functional movement disorders

It remains a fact that shifting attention away from something that naturally attracts attention is difficult. A possible way of improving that skill is by practicing meditation since meditation teaches to shift the attentional focus away from whatever the attentional focus might get attracted to.

We saw that performing a movement without giving it any importance leads to straighter trajectories in functional tremor patients. Another factor that might make it difficult for patients not to care about their movement and to shift their attentional focus away from it and its visual feedback is if the movement is of great importance to them. In many instances, the exactitude of a movement is in fact not of great importance. Helping patients realise that, will allow them to be more relaxed about their movements and allow their attention not to be drawn to them. It might be worth discussing what the worst outcome could be – in the case of a tremor a drink might get spilled, the handwriting might be illegible, when using a knife injury might occur. If the consequences are truly dangerous, then precautions must be taken, or the action must not be performed. If on the other hand the consequences are not too serious, then patients should be helped to put these into perspective and to realise that it is not worth worrying about them to the degree they might be. This might be particularly relevant in patients with perfectionist traits. A related issue is embarrassment and the worry about what other people might think. This was frequently reported as an aggravating factor by patients in this study. A potential strategy is to ask patients to put themselves in the other people's position and ask themselves whether they would think badly of another person because of their medical condition and mind his or her symptoms.

Finally, is there a role for placebo treatments in functional neurological disorders? The study showed that patients with FND are not more susceptible to placebo analgesia than healthy controls. If anything, they seem to be slightly less susceptible to it. On the other hand, given their symptoms are inherently changeable, placebo treatments can occasionally lead to major improvement or even cures. In many healthcare systems the issue of whether or not deceptive placebo treatments should be used is resolved by the fact that they are illegal. Should this be changed? Healthcare professionals will have strong opinions but ultimately, we should be guided by the patients' wishes, the additional professional knowledge and by the principle of *primum non nocere*. Although many patients might be generally in favour, a not insignificant percentage is strongly opposed, and that group of patients particularly needs to be taken into consideration. Overall the risk of deceptive placebo treatments, most importantly the risk of undermining trust in the medical profession, seems to represent a risk not worth taking. Open-label placebo offers the possibility of harnessing some of the aspects of the placebo effect without the deceptive component. Many patients will not be open to such an approach, but in those who are, open-label placebo, coupled with positive suggestion, could offer a treatment adjunct.

5.4 Wider implications

The study participants were primarily subjects with functional movement disorders, but many of the therapeutic implications are likely to be valid for patients with other types of functional neurological disorders; non-epileptic attack disorders for example, foreign accent syndrome, or functional vertigo.

Most healthy individuals have experienced situations, during which they paid particular attention to their movements and tried hard to make them "natural" or perfect, but instead provoked unnatural, awkward movements or behaviours. Common examples are public speaking, exams, acting, music, sports, trying to act naturally while being filmed, singing outside of the shower, or simply when trying to impress someone. Specific terms have even emerged in the field of sports: "choking under pressure", or the "yips" in golf, in which a professional golfer is suddenly unable to putt from a very short distance. It is likely that in these situations, healthy subjects do not let their movements happen automatically, but in an attempt to make them perfect, try to control them, thereby interfering in their implicit execution and ultimately rendering them abnormal. (Gallwey 1974).

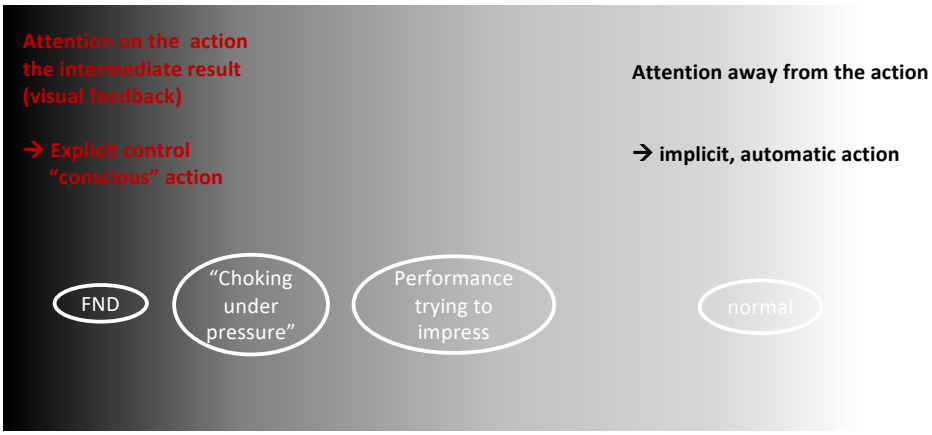


Figure 105: Functional neurological disorders and similar symptoms as a spectrum

Healthy individuals only experience these symptoms in a transitory way, typically under specific situations, such as under stress or pressure to perform well. In patients diagnosed with a functional neurological disorder on the other hand these abnormal symptoms persist.

The methods utilised to treat functional disorders can also be applied to healthy individuals or indeed professionals when faced with situations that are likely to trigger symptoms of this kind.

Unfortunately, some healthcare professionals have a tendency, not to take patients with functional symptoms as seriously as patients with equivalent organic disorders and some harbour the notion that the symptoms are exaggerated and somehow not real. This work shows that patients' beliefs

about the severity of their tremor are not inflated but accurate and not dissimilar to those of patients with an organic tremor. Similarly, their quantification of pain is not exaggerated, on the contrary, compared to healthy controls they have a tendency to underreport the intensity of pain. Finally, patients with a functional neurological disorder are not more suggestible in terms of placebo responses than healthy controls. Thus, it is more than time to rectify such misconceptions and destigmatise functional neurological disorders.

Since healthy individuals occasionally experience functional symptoms, rather than seeing functional neurological disorders as a strange aberration, one might regard them as an extreme form of common experience. They might be seen as a different shade of grey; similar to normal sadness and demotivation versus depression. So, in addition to it being time to destigmatise functional neurological disorders it might also be time to demystify them to some degree. After all, is there not a bit of hysteria in all of us?

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Appendices

A 1 Participant information & consent form

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The Pathophysiology of Functional Neurological Disorders (student study)

Project Reference Number: 16/0275. Participant Information Sheet: Version 3.0: 28/11/2018

We would like to invite you to take part in a research study that is currently taking place at University College London (Institute of Neurology and Institute of Cognitive Neuroscience). Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the study about?

We are trying to understand more about a group of neurological problems called functional neurological disorders, in particular functional movement disorders.
Movement disorders include conditions such as Parkinson's disease and tremor. Some patients with movement disorders have a recognised cause for the problem e.g. Parkinson's disease, but in others the cause is much less clear. These people are sometimes diagnosed with a *functional* movement disorder, and we are particularly interested in trying to understand how abnormal movements are generated in these people.
We are doing this by doing some special tests of how the parts of the nervous system that control movement are functioning. We are particularly interested in scientifically recording the abnormal movements, and seeing how some important systems that control movement (interaction of sensation and movement information, awareness of movement, attention, reaction time) are working. We plan to compare the results of tests in people with neurological disorders due to a known cause, those with functional neurological disorders, and people without any neurological disorder.

Why have I been contacted?

You have been contacted because you have been diagnosed with either a functional neurological disorder or an organic neurological disorder or because you have neither of those diagnoses and we would like to use your test results to compare them to people who have a functional or organic neurological disorder.

Where would the study take place?

All tests will take place at University College London, Queen Square, in central London.

What does the study involve?

There are a number of different tests that we are planning as part of this study. These are outlined below. We are not planning to perform all of them in each person. We have marked the box next to the part that we are inviting you to take part in at this time. Please note that none of the tests are invasive nor painful, and there is no need to restrict your lifestyle in any way. You will be given the opportunity to take regular breaks during the testing.

☐ Part 1: Questionnaires / test

In this part of the study we would like you to fill in a few questionnaires/tests. These are standard questionnaires/tests addressing things like mood, memory and movements. We would be grateful if you could fill these in at home. Should you, however, experience any difficulties, then we will complete them together at the end of the other studies. It should take less than an hour. An additional questionnaire involving your opinion on treatments will be given to you before or after the study.

☐ Part 2: Assessing factors involved in movement generation and control

This part of the study looks at factors that influence how our brain generates and controls movements. We are trying to find out how these factors might be implicated in functional neurological disorders.
In order to do this we would like you to make simple movements, such as a reaching movement, either in isolation, or while performing other simple psychophysical tasks that will be displayed on a computer screen and require verbal or key press responses.
We will record your movements with non-invasive methods and your muscular activity with the help of surface electromyography. Surface electromyography is entirely pain-free and non-invasive, and there are no contraindications to it. It involves making recordings from your muscles by using electrodes (little wires) that are taped to the skin over your muscles. No needles are used.
This part of the study will last 1 - 2 hours.

☐ Part3: Assessing factors involved in the perceived timing of movements

We would like to examine how you perceive the timing of your own movements. This type of study lets us get a picture of how aware you are of how it is working. The way in which we perceive our own movements is important in the accurate control of movement, and we are interested in how this process might be affected in people with functional neurological disorders. This part of the study will involve you sitting in front of a computer screen. We will ask you to make movements in response to cues given on the computer screen. We will also ask you to judge the interval between your movement and a sound delivered over headphones. This part of the study will last ½ - 1 hour.

☐ **Part 4: Videotaping of your movements, excluding the face**

In some cases we would like to film your movements. Please note that we will not film your face, unless you give us explicit permission to do so (below). The video will only be shown to the researchers in this study. The video will be stored securely and not shown to anyone else, unless you have given written permission.

☐ **Part 5: Videotaping of your movements, including the face**

In some cases we would like to film your movements, including your face. The video will only be shown to the researchers in this study. The video will be stored securely and not shown to anyone else, unless you have given written permission.

☐ **Part 6: functional Magnetic Resonance Imaging (fMRI)**

In this part of the study we would like to repeat simple movement and cognitive tasks, similar to those performed in part 2, while scanning your brain using functional MRI. This will allow us to see which specific brain areas are activated by those tasks. It will help us understand how the brain generates and controls movements or how functional neurological symptoms are generated.

Magnetic Resonance Imaging (MRI) is a bit like an X-ray machine, but it does not use X-rays or any ionising radiation, but instead magnets to image the brain. MRI is painless and safe, as long as people with any magnetic metal implants (such as pacemakers) are excluded. Before being invited to the centre we will check that you are suitable for scanning using MRI and we will check this again, just before your session.

One sort of brain scan involves taking detailed anatomical images of your brain – a structural scan. While structural images of your brain are made, you will be asked to relax and keep still. During another type of scan, known as a functional MRI (fMRI) scan, you will do the movement or cognitive tasks you practised before entering the scanner.

Before scanning, you will be shown exactly what you have to do, and given time to practise. Once you have removed any metal you are wearing or carrying, you will be asked to lie on a table inside the scanner for up to 60 minutes while you perform the tasks you had practised before and while the images of your brain are made. We will be able talk to you between scans while you are inside the scanner. After scanning, we may ask you a number of questions about your experience of doing the tasks during the scan. This part of the study will take about 2 hours.

Are there any side effects of fMRI?

During scanning, the scanner is very noisy. To reduce the noise, you will either wear ear plugs, or headphones that are designed to reduce the noise impact of the scanner. Some people find the enclosed space of the scanner uncomfortable. You will have access to a panic button at all times and can press this to stop the scan and you will immediately be taken out of the scanner.

What happens if an unexpected abnormality is seen on the MRI?

Please note that this MRI is purely for research purposes. It is different from clinical MRI scanning and will not be shown to a radiologist. We will therefore not be liable for any unnoticed minor or medium degree abnormalities. However, should the MRI scan unexpectedly reveal a clinically relevant abnormality that was noticed, then we will inform yourself and your GP of this finding. If you prefer not to be informed of an image anomaly, you must choose not to participate in this part of the study.

☐ **Part 7: Pain rating**

We would like to evaluate the rating of mild to moderate pain and will therefore ask you to judge the intensity of painful and non-painful electro-tactile stimuli.

Surface electrodes with gel will be taped to two small areas of your skin on your limbs. These electrodes allow the passage of electricity, which initially leads to a tingling sensation and as the intensity is increased, gradually causes mild pain. Further increases can lead to stronger pain. The stimuli are similar to those routinely used in nerve conduction studies, which you might have had in the past. Note that the stimulation gives a very short pulse, so that the sensation only lasts very briefly. Because the stimuli are intended to be mildly to moderately painful, they may cause you some discomfort. However, before starting the experiment, we will carefully measure your pain and sensation thresholds. We will increase the intensity very gradually until you perceive it as mildly to moderately painful, but no further. We will endeavour to keep you as comfortable as possible at all times. You are free not to take part in this part of the study or to interrupt the study at any time if you wish to.

We might also apply a strong painkiller / anaesthetic cream, an inactive cream or a placebo so as to evaluate their effects. Please inform us if you have any allergies.

Because of theoretical risks you should not participate in this part of the study if you have a cardiac pacemaker, deep brain stimulator or other implanted electronic devices.

IMPORTANT INFORMATION FOR EVERYONE

What are the possible benefits of taking part?

There is not likely to be any direct benefit to you from taking part in this study. We hope that the increased understanding of functional neurological disorders gained from this study will help us to plan better treatment for the future.

What are the possible disadvantages to taking part?

Apart from the potential side effects detailed under each aspect of the study above, we do not envisage any particular disadvantages to your taking part in this study. The study will involve spending some at University College London, but we will try to offer times for the studies which are convenient to you. As a small compensation you will be given £7.50 per hour you spend doing the study at University College London.

What happens if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns regarding this study, then these should be directed to Prof Kailash Bhatia, or to the complaints manager at UCL, quoting the study number at the top of the first page.

What will happen to the results of the research study?

Once we have included a sufficient number of participants in the study we will analyse all the data and will attempt to draw conclusions about the way in which the nervous system is malfunctioning in people with functional neurological disorders. We hope to publish our findings in scientific journals and present them at scientific conferences. The identities of individual participants would not be included in any such publication or presentation.

Will I be informed of the results of the study?

If you wish to receive a copy of the published scientific paper, please indicate so on the consent form.

Who is funding the research?

The research costs for this study are paid by a Clinical Research Training Fellowship from the Association of British Neurologists / Patrick Berthoud Charitable Trust.

Withdrawal from the project

Your participation in the trial is entirely voluntary. You are free to decline to enter or to withdraw from the study any time without having to give a reason. This will in no way affect your clinical care.

Who has reviewed the study?

This study has been reviewed by the London - Bromley Research Ethics Committee.

What will happen to the information about me that is collected? Who will have access to it?

This research study will collect a number of pieces of information about you. We will keep this information secure and will pseudonymise it. This means that we will code all information so that it can only be linked to your name via a specific key held in a very secure location, and we will ensure that confidentiality is strictly maintained. All information regarding your

medical history will be treated as strictly confidential and will only be used for research purposes.

All the information (apart from the paper questionnaires/tests) will be stored in the departmental secure storage system, a system that meets data protection requirements. The controller of the data (i.e. the organisation collecting, storing, handling and processing the information) will be University College London. The paper questionnaires/tests will be securely stored in a locked location within University College London. As principal investigator, Professor Bhatia will be responsible by law for the safety and security of this information. No other organisations or researchers will have access to the data without his permission and if this were allowed it would be in a coded form (so that the identity of the people involved would remain anonymous).

The new General Data Protection Regulation (**GDPR**) requires us to inform you further about the use of your personal data. Please consult UCL's GDPR privacy notice: https://www.ucl.ac.uk/legal-services/privacy/participants-health-and-care-research-privacy-notice

For patients only (i.e. this does not concern you if you are a healthy control), in view of the GDPR, the NHS Health Research Authority requires us to give you this additional information concerning the use of your data:

University College London (UCL) is the sponsor for this study based in the United Kingdom. We will be using the information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. University College London will keep identifiable information about you for three years after the study has finished, the only exception to this are the functional MRI images (if performed) which will be kept for 10 years.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

University College London will use your name and contact details to contact you about the research study, and oversee the quality of the study. Individuals from University College London and regulatory organisations may look at your research records to check the accuracy of the research study. The National Hospital for Neurology and Neurosurgery or St George´s Hospital, respectively, will pass these details to University College London along with the information collected from you. The only people in University College London who will have access to information that identifies you will be people who need to contact you to ask you to participate and organise a date, or audit the data collection process.

Contact for further information

Please feel free to contact Dr Huys for any further information about the study:
Dr Anne-Catherine Huys
Department of Clinical and Movement Neurosciences
UCL Queen Square Institute of Neurology
33 Queen Square, floor 6, London, WC1N 3BG
Tel: (+44) 20 3448 8605
anne-catherine.huys.15@ucl.ac.uk

Other investigators on this study:

Chief investigator :

Professor Kailash Bhatia
Department of Clinical and Movement Neurosciences
UCL Queen Square Institute of Neurology
National Hospital for Neurology and Neurosurgery
Queen Square, London, WC1N 3BG

Other investigators on this study are: Professor Mark Edwards (St George's University and St George's Hospital), Professor Patrick Haggard (Institute of Cognitive Neuroscience, UCL), and Professor Ray Dolan (Wellcome Trust Centre for Neuroimaging, Institute of Neurology, UCL).

Thank you!

Whether or not you decide to **participate** in the study, we would like to thank you for taking the time to read this information sheet – we very much appreciate it.

Nb. Should you agree to take part in the study, you will be given a copy of this information sheet to keep as well as a signed copy of the consent form

Department of Clinical and Movement Neurosciences
UCL Queen Square Institute of Neurology
Queen Square
London WC1N 3BG

Title of Project:
The Pathophysiology of Functional Neurological Disorders (student study)

Project Reference Number: 16/0275
Neurology Patient Consent form: Version 3.0: 28/11/2018

Name of Researchers: Dr Anne-Catherine Huys, Professor Kailash Bhatia, Professor Mark Edwards, Professor Patrick Haggard.

CONSENT FORM

Please initial box

1. I confirm that I have read the information sheet dated 28/11/2018 (version 3.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I confirm that I will participate in the following parts of the study:
   - Part 1: Questionnaires / test ☐
   - Part 2: Assessing factors involved in movement generation and control ☐
   - Part 3: Assessing factors involved in the perceived timing of movements ☐
   - Part 4: Videotaping of my movements, *excluding* the face ☐
   - Part 5: Videotaping of my movements, *including* the face ☐
   - Part 6: functional Magnetic Resonance Imaging ☐
   - Part 7: Pain rating ☐
     I confirm that I do **not** have a pacemaker, deep brain stimulator or any other implanted electronic device ☐

3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

4. I understand that relevant sections of my medical notes and data collected during the study may be looked at by Dr Huys, and either Professor Edwards or Professor Bhatia, depending on who is my treating neurologist. ☐

5. I understand that the data collected in this study, once anonymised, so that my identity cannot be identified, might be published in scientific journals, presented at scientific conferences, and shared with other researchers. ☐

6. I agree to my General Practitioner being informed of my participation in the study in the case of an incidental finding that could have implications on my health. ☐

7. I agree to take part in the above study. ☐

Additional option in case of videotaping:

8. I agree to the videotape of myself, on which my face is not visible, to be used for research and educational purposes, including possible publication in print or online in medical journals.

Name of Participant	Date	Signature
Anne-Catherine Huys		
Name of Person taking consent	Date	Signature

Please tick this box if you do **not** wish to be contacted again for further parts of this study ☐

Please write your e-mail address here, if you wish to receive a copy of the published scientific paper in which you participated.

A 2 Questionnaires

A 2.1 General questionnaire

Department of Clinical and Movement Neurosciences
UCL Queen Square institute of neurology
Queen square
London WC1N 3BG

General questionnaire

1. Please enter your age _____ and gender _____

2. Handedness right handed left handed ambidextrous

3. What level of education did you achieve?

   O-levels GCSE A-levels higher education
   If higher education, please state how many years: _____

4. Please list any neurological diagnosis you have (apart from migraines and tremor):

   _____
   _____

5. Do you have any migraines? yes no

   a. Does light bother you?

      yes all the time only when I have a migraine never

   b. Does noise bother you?

      yes all the time only when I have a migraine never

6. Please list your medication, including the doses:

   _____
   _____
   _____
   _____

i. For how many years have you had the abnormal movements?

_____

ii. Which side is more affected?

left right same on both sides

iii. What are your symptoms (what is the exact diagnosis) ?

_____

iv. What makes your symptoms worse?

_____
_____
_____
_____

v. What makes your symptoms better?

_____
_____
_____
_____

vi. Do your symptoms improve when you drink alcohol?

Yes no

1. If yes, after how many units of alcohol _____

Note that this questionnaire was slightly adapted to the different study populations. For the tremor study, “abnormal movements” or “symptoms” were replaced by “tremor”.

A 2.2 Hospital Anxiety and Depression Scale

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

A 2.3 Masters' movement specific reinvestment scale

THE MOVEMENT SPECIFIC REINVESTMENT SCALE

Name: _____ Date: _____ Age: _____ Hand: L / R

DIRECTIONS: Below are a number of statements about your movements. The possible answers go from 'strongly agree' to 'strongly disagree'. There are no right or wrong answers so circle the answer that <u>best</u> describes how you feel for each question.

1 I rarely forget the times when my movements have failed me, however slight the failure.

strongly disagree	moderately disagree	weakly disagree	weakly agree	moderately agree	strongly agree

2 I'm always trying to figure out why my actions failed.

strongly disagree	moderately disagree	weakly disagree	weakly agree	moderately agree	strongly agree

3 I reflect about my movement a lot.

strongly disagree	moderately disagree	weakly disagree	weakly agree	moderately agree	strongly agree

4 I am always trying to think about my movements when I carry them out.

strongly disagree	moderately disagree	weakly disagree	weakly agree	moderately agree	strongly agree

5 I'm self conscious about the way I look when I am moving.

strongly disagree	moderately disagree	weakly disagree	weakly agree	moderately agree	strongly agree

6 I sometimes have the feeling that I'm watching myself move.

strongly disagree	moderately disagree	weakly disagree	weakly agree	moderately agree	strongly agree

7 I'm aware of the way my mind and body works when I am carrying out a movement.

strongly disagree	moderately disagree	weakly disagree	weakly agree	moderately agree	strongly agree

8 I'm concerned about my style of moving.

strongly disagree	moderately disagree	weakly disagree	weakly agree	moderately agree	strongly agree

9 If I see my reflection in a shop window, I will examine my movements.

strongly disagree	moderately disagree	weakly disagree	weakly agree	moderately agree	strongly agree

10 I am concerned about what people think about me when I am moving.

strongly disagree	moderately disagree	weakly disagree	weakly agree	moderately agree	strongly agree

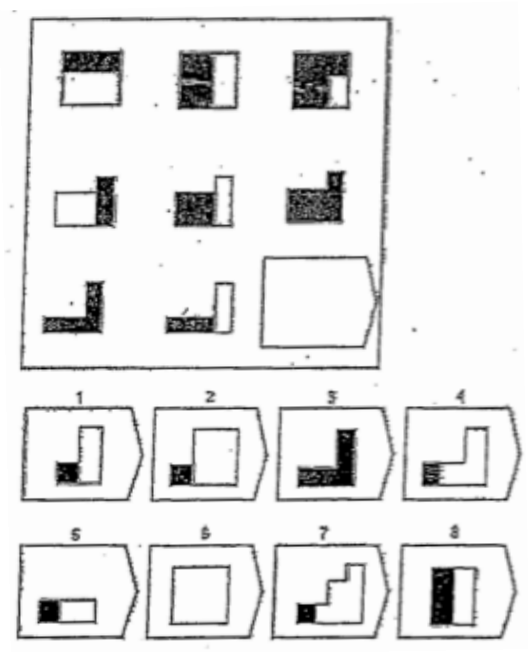
A 2.4 Raven's progressive matrices

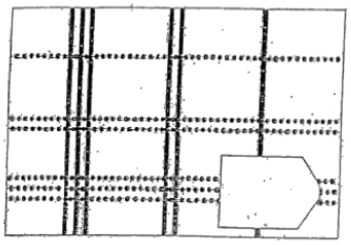
Instructions:

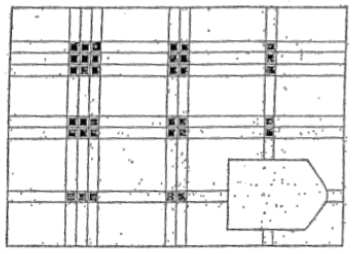
The test items on the following pages are designed to test reasoning skills. There are 12 items in total for which you should not take longer than 30 minutes. Your task is to identify the missing element that completes the pattern shown at the top of each page.

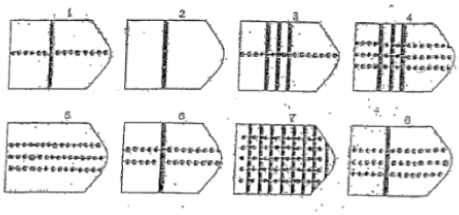
Here is an example:
Your task is to identify, which of the 8 elements shown below would complete the pattern shown in the top square.

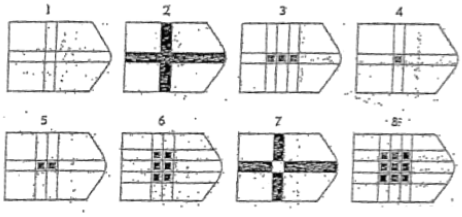
In this particular case, the correct element would be number 3. This is because in row 1, all three elements are square-shaped. In row 2, all three elements are a rectangle with an extra corner on the top right side. In row 3, both shapes are thin L-shapes, with either side being equally long, and number 3 would be the only suitable answer (the sides of number 1 are not equally long, and the sides of number 4 are too thick).

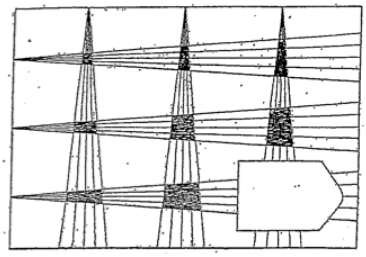


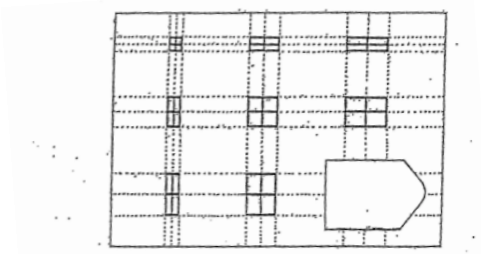


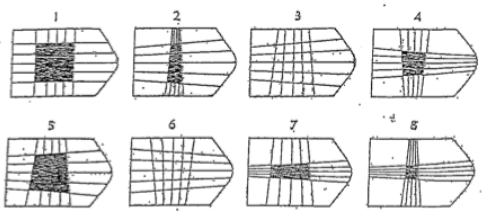


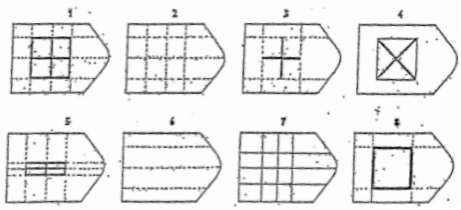


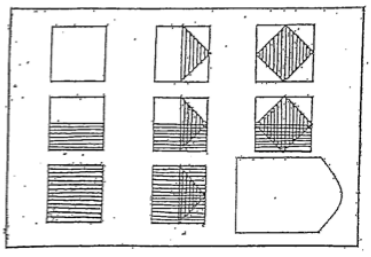


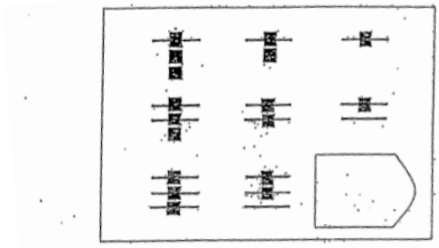


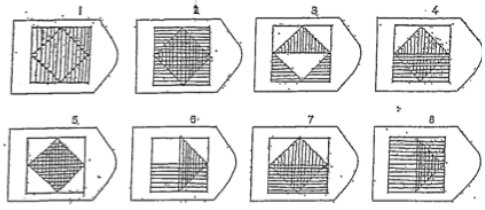


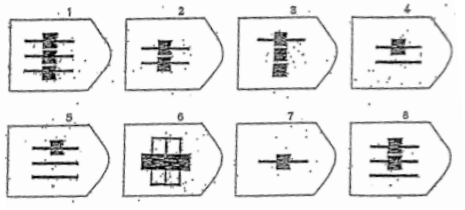


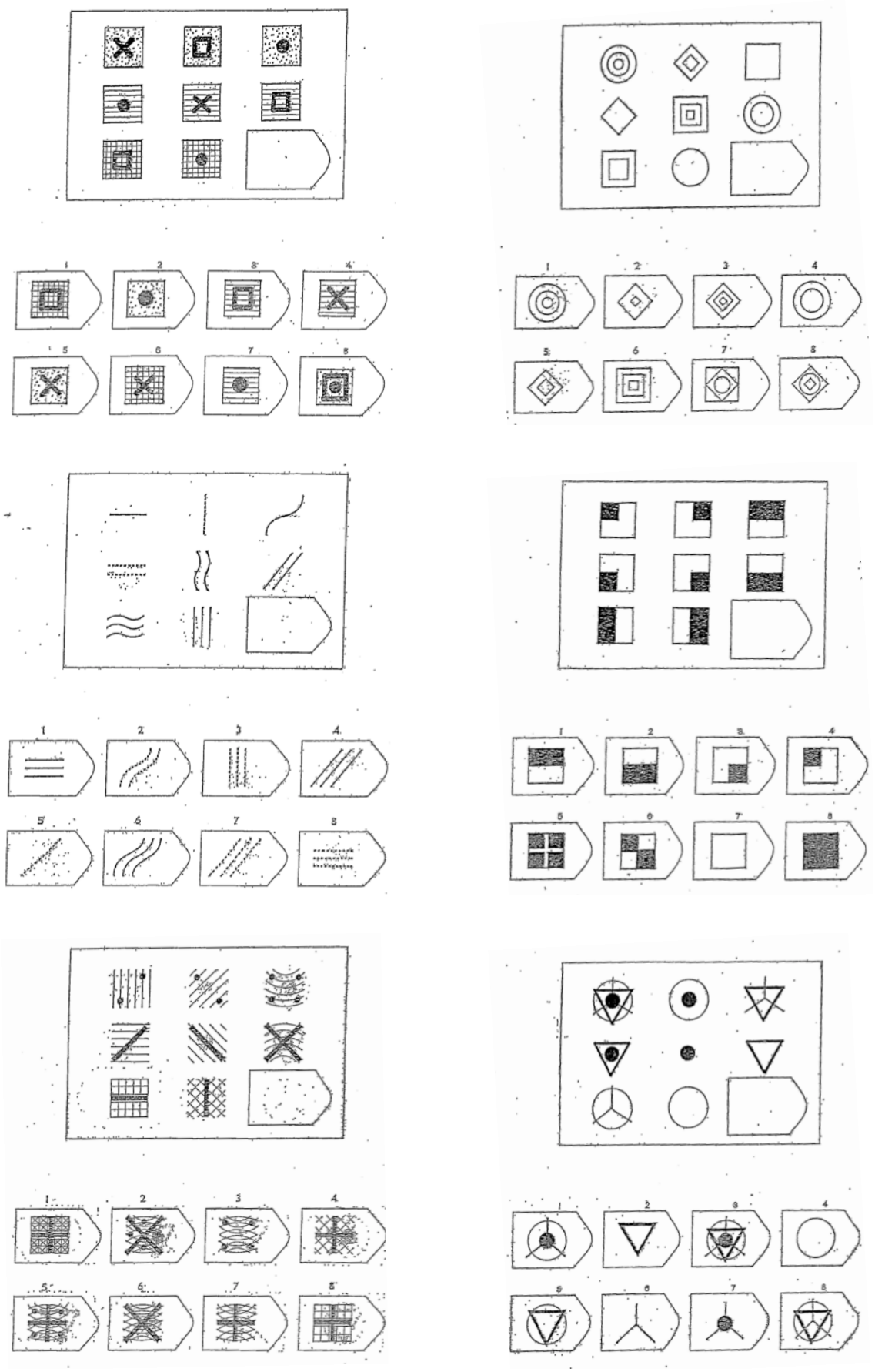












A 3 ANT

A 3.1 Instructions

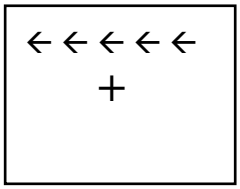
This is an experiment investigating attention. You will be shown a central arrow on the screen pointing either to the left or to the right (for example ← or →). The arrow will be surrounded either by 4 lines or by 4 arrows (2 on either side).

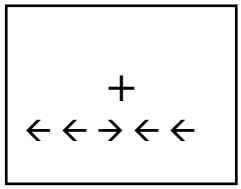
Your task is to press the left arrow key on your keyboard when the **central** arrow points left and the right arrow key when the central arrow points right. On some trials, the central arrow will be flanked by straight lines, on others by four arrows pointing in the same or in the opposite direction, for example:

— —← — — or ← ← ← ← ← or → → ← → →

Your task is to respond to the direction only of the **CENTRAL arrow**. Use your left index finger for the left arrow key and your right index finger for the right arrow key. Please make your response as quickly and accurately as possible. Your reaction time and accuracy will be recorded.

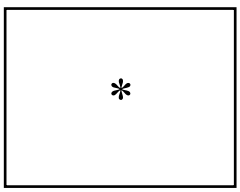
There will be a cross (+) in the centre of the screen and the arrows will appear either above or below the cross. You should try to fixate on the cross throughout the experiment. Please do not move your eyes to the arrows.

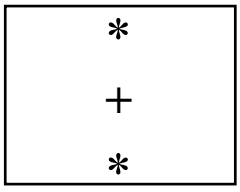




On some trials there is no warning, on others there will be **asterisk cues (*) indicating when or where the arrow will occur**:

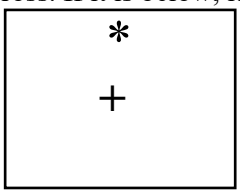
- If the cue is at the centre or both above and below fixation it indicates that the arrow is about to appear, but it does not say where it will appear.



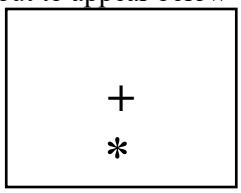


→ arrows about to appear (above or below)

- A single asterisk cue above the fixation cross indicates that the arrow is about to appear above the fixation cross. If it is below, it means it is about to appear below



→ arrows about to appear <u>above</u>



→ arrows about to appear <u>below</u>

Do rely on the asterisk cues as they are 100% correct. Try to maintain fixation at all times. However, you may attend when and where indicated by the cues.

A 3.2 Size of stimuli

	Visual angle (in degrees, rounded to 2 decimal places)
Arrow	
Total arrow length	0.55º
Arrow line length	0.37º
Arrow line width	0.06º
Triangle base	0.18º
gap between arrows	0.06º
All 5 arrows with gap	3.08º
Location above or below fixation	1.06º
Fixation cross (+) and cue (*)	
Length of the line	0.34º
Thickness of line	0.03º
Text	
vertical size of capital letter	0.34º

Table 92: Stimuli sizes in visual angles
The stimuli are presented on a 19-inch screen, with a refresh rate of 75Hz at a viewing distance of 65cm.

A 3.3 Excluding subjects on relevant medication

So as to exclude that the group differences were due to medications, the analyses were repeated after excluding any subject on any daily medication that might have an effect on attention: any benzodiazepine, opioid, antidepressant, antiepileptic, neuroleptic or anticholinergic. This also excluded any subjects whose anxiety, depression or pain was important enough to warrant treatments. Note that the three organic tremor patient and the one FND patient who were taking the beta-blocker propranolol on a daily basis, were not excluded as there is no evidence for propranolol affecting attention (Brooks et al. 1988; Steenbergen et al. 2015).

Overall RT

The overall RT in all subjects not on any relevant medication showed a trend to a difference between the three groups (Kruskal-Wallis test ($\chi^2(2) = 5.73$, $p = .057$, $\eta^2 = .061$), with Šidák-Holm corrected, two-sample t-tests showing a significant difference between the FMD group ($M = 731.6$ms, $SD = 175.2$) and the healthy controls ($M = 604.4$ms, $SD = 97.8$) ($t_{uncorr}(39)=-3.00$, $p_{corr}=.0094$, $d=-0.99$) and between the FMD group and the organic controls ($M = 629.2$ms, $SD = 97.9$), ($t_{uncorr}(35) = -2.29$, $p_{corr} = .028$, $d = -0.78$).

Alerting, orienting and conflict

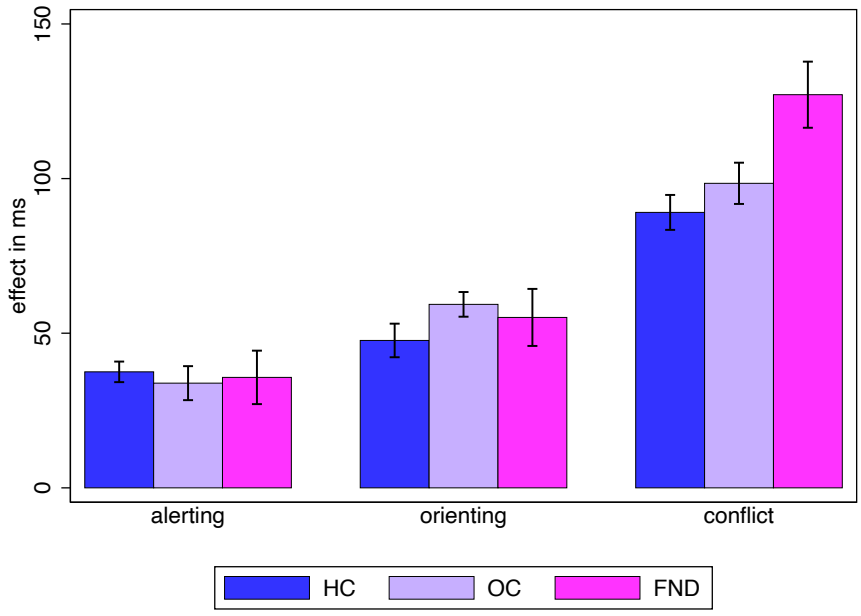


Figure 106: Alerting, orienting and conflict effect of subjects on no relevant medication

	Shapiro-Wilk normality test		
	Alerting	**Orienting**	**Conflict**
HC (n=27)	0.88	0.64	0.16
OC (n=23)	0.85	0.77	**0.0080**
FND (n=14)	0.23	**0.013**	0.94
Levene	**0.0098**	0.15	0.30

Table 93: Shapiro-Wilk normality test and Levene's test of homogeneity of variance (excluding subjects on relevant drugs)

Since the alerting effect did not have equal variances between the three groups, the orienting and conflict effect each contained one group that had non-normally distributed values, and the sample sizes of the three groups were unequal, the assumptions of a one-way ANOVA were not met and so the non-parametric Kruskal Wallis test was performed instead.

	Alerting (*sd*)	**Orienting** (*sd*)	**Conflict** (*sd*)
HC (n=27)	37.5 (17.3)	47.7 (28.2)	89.1 (29.4)
Org (n=23)	33. (26.4)	59.3 (19.1)	98.5 (32.0)
FND (n=14)	35.7 (32.3)	55.1 (34.5)	127.1 (40.0)
Kruskal Wallis	$\chi^2(2)=0.70$	$\chi^2(2)=2.49$	$\chi^2(2)=8.83$
	$p = .70$	$p = .29$	***p* = .012**

Table 94: Alerting, orienting & conflict effect group averages (excluding subjects on relevant drugs)

Kruskal-Wallis test was not significant for the alerting, nor orienting effect, but was significant for the conflict effect. Šidák-Holm corrected, two-sample t-test confirmed that there was a significant difference between the FND group and the healthy controls ($p = .0026$). Similarly, Šidák-Holm corrected two-sample Wilcoxon rank-sum test gave a significant difference between the FND group and the organic controls ($p = .024$).

A 4 Natural attentional focus

A 4.1 Participants' age and acuity

	Age average (range)	**M:F**	**Visual acuity** average (*sd*) (range)
HC (n=24)	42.9 (21-68)	10:14	95.8 (8.8) (70-100)
OT (n=21)	53.6 (21-78)	11:10	99.5 (2.2) (90-100)
FND (n=25)	51.8 (21-75)	11:14	87.8 (17.4) (50-100)
One-way ANOVA	$F(2,67)=3.16$		
	***p* = .0489**		
Kruskal-Wallis			$\chi^2(2)$ with ties = 9.2
			***p* = .0099**

Table 95: Participants' characteristics for the deviation and target jump conditions

The healthy controls´ ages were not normally distributed, the other groups´ were. There was, however, homogeneity of variance between the three groups (Levene´s p = .23). A one-way ANOVA was therefore performed and was just significant at p = .0489. However, none of the post hoc Šidák-Holm corrected p-values were significant (two-sample Wilcoxon rank sum test for HC versus FND: p = .091, HC versus OT p = .091 and two-sample t-test for FND versus OT: p = .70).

Acuity was not normally distributed for either group, nor was there equality of variance between the groups (Levene's p< .0001). A Kruskal-Wallis test was therefore performed, which was significant. Post-hoc Šidák-Holm corrected two-sample Wilcoxon rank sum test was significant for the FND versus OT comparison (p = .0084) but not for the FND versus HC comparison (p = .088).

In summary, the ages were not significantly different between the groups. However, the binocular corrected visual acuity was significantly worse in the FND group compared to the OT group but not compared to the HC group.

	Age average (range)	**M:F**	**Visual acuity** (*sd*) (range)
HC (n=27)	43.6 (21-79)	12:15	95.6 (13.9) (32-100)
OT (n=22)	52.0 (21-78)	14: 8	98.0 (5.5) (80-100)
FND (n=28)	51.6 (21-74)	13:15	90.0 (14.4) (50-100)
One-way ANOVA	$F(2,74)=2.49$		
	$p = .090$		
Kruskal-Wallis			$\chi^2(2)$ with ties= 7.05
			***p* = .030**

Table 96: Participants' characteristics for the luminance conditions

In view of the normal distribution for all group ages and the absence of inequality of variance, one-way ANOVA was performed, which revealed no significant difference between the groups. Visual acuity was not normally distributed, nor was there equality of variance between the groups (Levene $p = .0029$), therefore Kruskal-Wallis rank test was performed. Šidák-Holm adjusted *p*-values in view of multiple comparisons for the two-sample Wilcoxon rank-sum test were just not significant for the FND compared to either control group ($p = .051$ in both cases).

In summary, neither age nor visual acuity were significantly different between the three groups.

A 4.1 Number of trials

Detection threshold	
Added deviation Target jump Target luminance change Cursor luminance change threshold conditions	***Spontaneous detection threshold***: Amplitude increased by 1 pixel for the target jump; by 1 ° for the deviation; or by [0.05, 0.05, 0.05] in the red green blue colour model ([R,G,B]) for the luminance change respectively, on each successive trial until detected. ***Absolute detection threshold:*** 2x as for spontaneous detection threshold ***Threshold for 75% correct answers:*** repeated up to 4x until amplitude found that lead to 60 to 80 % correct detection. If on these 4 rounds the detection was either 100% or < 60 % then the amplitude for 100% detection was chosen by the examiner. (Practice round: 8 trials in total, 3 no-jump, 5 jump. If detected 3/5 or 4/5 target jumps, that amplitude was taken as the 75% correct value. If the target jump condition had been done first and subjects were able to detect 100% of the 1pixel jumps, which were the smallest possible jumps, then the value with 100% correct detection was also accepted and used for all subsequent added deviation conditions.)

Table 97: Number of trials for the detection threshold conditions

A 4.2 Target versus cursor luminance change instructions

Cursor or target colour change

Instructions

As you move towards the target, one of 4 things will happen:

- The cursor (the moving dot) will briefly change in brightness
- The target will briefly change in brightness
- Both the cursor and the target will both briefly change in brightness
- Neither of them will change in brightness, nothing will happen.

After having reached the target, you will be asked to reply to 2 questions

- Did the cursor (the moving dot) change in brightness? Answer yes or no
- Did the target change in brightness? Answer yes or no

This will be repeated several times.

Please perform the movement as you would normally, as if there was nothing to look out for. I do not want you to move really slowly and keep looking back and forth

between the cursor and the target. Instead, do the movement as if there was nothing to look out for and simply say what springs out.
Feel free to ask any questions, otherwise you may begin.

A 5 Attentional manipulations

A 5.1 Order of conditions

The order of the conditions was randomised from subject to subject as far as possible given the following constraints:

The very first condition was always a baseline condition, either with or without the box. Within the box on or box off conditions respectively, the baseline condition was always the first condition.

For practical setup reasons, all the box off conditions were performed in one block (with the exception of the repetition of the baseline box off condition if the entire experiment began with the baseline box off condition). Within the "box on" and "box off" blocks, the first condition was always the respective baseline condition.

The implicit attentional manipulation conditions to the target, to the visual feedback or to the movement respectively, were always performed immediately after the respective detection threshold was determined, as described in the "Natural attentional focus" section 2.2 ("deviation", "target jump", "target luminance", of "cursor luminance" threshold conditions respectively). This was done so as to minimise potential confusion between the tasks.

A 5.2 Number of trials

	Total number of trials
At the beginning box off	30
At the beginning box on	25-40
At the end box off / on	20

Table 98: Number of trials for the baseline condition

Attentional manipulation	Number of trials
Onto the movement	
Explicit Box off Box on	15
Implicit: Deviation/no-deviation	18-24
Accuracy	15
Onto somatosensation	15
Onto the target	
Explicit Box off Box on	15
Implicit: Target jump / no jump Target luminance change	 18-24 40
onto the target and beyond	36-40
Auditory distraction	36
Absent visual feedback	15
onto visual feedback (cursor luminance change)	40
Slow / fast	10
"To start"	24

Table 99: Number of trials for the attentional manipulation conditions

A 5.3 Characteristics of study participants

The best visual acuity (with or without correction) was measured with a hand-held Snellen chart.

The severity of each subject´s postural tremor was clinically rated in four categories: very mild, mild, moderate or severe and the maximum amplitude of the tremor was estimated clinically.

The following tables summarises the characteristics of the study participants of each one of the attentional manipulation conditions.

•		Action tremor			Age average (range)	M:F	Visual acuity
		Type	**Severity**	**Duration**			
Box off (direct visual feedback) & auditory distraction	**HC** (n=20)	-	-	-	44.0 (21-68)	9:11	95.0%
	OT (n=19)	DT: 14 ET: 4 WD: 1	Very mild: 4 Mild: 12 Moderate: 3 Severe: 0	23.6y	53.3 (21-78)	10:9	99.5%
	FND (n=17)	functional: 17	Very mild: 1 Mild: 7 Moderate: 7 Severe: 2	6.7y	53.1 (23-75)	8:9	89.0
	One-way ANOVA				$F(2,53)=2.06$ $p = .14$		$F(2,55)=4.40$ **$p = .017$**
	Chi-square goodness of fit		$\chi^2(3)=6.63$ $p = .085$			$\chi^2(2)=0.24$ $p = .88$	
	Two-sample t-test			**$p = .0004$**			

Table 100: Participants' characteristics for any condition involving an direct visual feedback condition (box off) and the auditory distraction condition
With the corresponding statistical tests. DT: dystonic tremor, ET: essential tremor, WD: Wilson disease.

Two-sample t-test is for the acuity was significant for the comparison FND group versus OT group ($p = .009$), but not for the FND group compared to the healthy controls ($p = .16$).

		Action tremor			Age average (range)	M:F	Visual acuity
		Type	**Severity**	**Duration**			
Luminance change (cursor, target)	**HC** (n=18)	-	-	-	45.0 (21-79)	7:11	94.5
	OT (n=22)	DT: 19 ET: 2 WD: 1	Very mild: 6 Mild: 12 Moderate: 3 Severe: 1	22.9	52.0 (21-78)	14: 8	98.0
	FND (n=11)	functional: 11	Very mild: 5 Mild: 1 Moderate: 5	7.6	49.8 (21-74)	5:6	89.1
	One-way ANOVA				$F(2,48)=0.88$ $p = .42$		$F(2,48)=1.80$ $p = .18$
	Chi-square goodness of fit		$\chi^2(3)= 4.9$ $p = .29$			$\chi^2(2)=2.60$ $p = .27$	
	Two-sample t-test			***p* = .009**			

Table 101: Participants' characteristics for the luminance change conditions
With the corresponding statistical tests. DT: dystonic tremor, ET: essential tremor, WD: Wilson disease.

		Action tremor			Age average (range)	M:F	Visual acuity
		Type	**Severity**	**Duration**			
Implicit attention (to proprio-ceptive motor or target)	**HC** (n=23)	-	-	-	42.7 (21-68)	9:14	95.7%
	OT (n=21)	DT: 16 ET: 4 WD: 1	Very mild: 3 Mild: 12 Moderate: 4 Severe: 1	23.3y	53.6 (21-78)	11:10	99.5%
	FND (n=21)	functional: 21	Very mild: 2 Mild: 9 Moderate: 7 Severe:0	6.5y	51.0 (21-75)	9:12	92.9%
	One-way ANOVA				$F(2,62)=2.82$ $p = .067$		$F(2,62)=2.65$ $p = .079$
	Chi-square goodness of fit		$\chi^2(3)=3.78$ $p = .58$			$\chi^2(2)=0.82$ $p = .66$	
	Two-sample t-test			***p* < .0001**			

Table 102: Participants' characteristics for the implicit attention to the proprioceptive aspect of movement and implicit attention to the target conditions
With the corresponding statistical tests. DT: dystonic tremor, ET: essential tremor, WD: Wilson disease.

		Action tremor			Age average (range)	M:F	Visual acuity
		Type	**Severity**	**Duration**			
Explicit attention Box on (to movement or target)	**HC** (n=20)	-	-	-	44.0 (21-68)	9:11	
	OT (n=21)	DT: 16 ET: 4 WD: 1	Very mild: 3 Mild: 12 Moderate: 4 Severe: 1	23.3y	53.6 (21-78)	11:10	
	FND (n=19)	functional: 19	Very mild: 2 Mild: 7 Moderate: 7 Severe: 0	6.3y	52.2 (23-75)	8:11	
	One-way ANOVA				$F(2,57)=2.11$ $p = .13$		$F(2,57)=2.97$ $p = .059$
	Chi-square goodness of fit		$\chi^2(3)= 4.58$ $p = .47$			$\chi^2(2)=0.46$ $p = .80$	
	Two-sample t-test			***p* = .0002**			

Table 103: Participants' characteristics for the explicit attention conditions with indirect visual feedback
With the corresponding statistical tests. DT: dystonic tremor, ET: essential tremor, WD: Wilson disease.

		Action tremor			Age average (range)	M:F	Visual acuity
		Type	**Severity**	**Duration**			
Slow / fast	**HC** (n=19)	-	-	-	44.8 (21-68)	9:10	94.7%
	OT (n=20)	DT: 15 ET: 4 WD: 1	Very mild: 4 Mild: 12 Moderate: 4 Severe: 0	24.3y	52.8 (21-78)	11:9	99.5%
	FND (n=19)	functional: 19	Very mild: 2 Mild: 7 Moderate: 9 Severe: 1	6.3	52.2 (23-75)	8:11	91.4%
	One-way ANOVA				$F(2,55)=1.47$ $p = .24$		$F(2,55)=2.81$ $p = .069$
	Chi-square goodness of fit		$\chi^2(3)= 4.88$ $p = .18$			$\chi^2(2)=66$ $p = .72$	
	Two-sample t-test			***p* < .0001**			

Table 104: Participants' characteristics for the slow and fast conditions
With the corresponding statistical tests. DT: dystonic tremor, ET: essential tremor, WD: Wilson disease.

		Action tremor			Age average (range)	M:F	Visual acuity
		Type	**Severity**	**Duration**			
Beyond the movement	**HC** (n=23)	-	-	-	45.0 (21-79)	9:14	95.7%
	OT (n=20)	DT: 15 ET: 4 WD: 1	Very mild: 4 Mild: 12 Moderate: 4 Severe: 0	22.7y	52.0 (21-78)	10:10	99.5%
	FND (n=19)	functional: 19	Very mild: 0 Mild: 12 Moderate: 6 Severe: 1	6.8y	49.8 (21-74)	9:10	91.4%
	One-way ANOVA				$F(2,59)=3.0$ $p = .057$		$F(2,59)=2.93$ $p = .061$
	Chi-square goodness of fit		$\chi^2(3)= 5.38$ $p = .15$			$\chi^2(2)=0.56$ $p = .75$	
	Two-sample t-test			**$p = .0004$**			

Table 105: Participants' characteristics for the beyond the movement condition
With the corresponding statistical tests. DT: dystonic tremor, ET: essential tremor, WD: Wilson disease.

		Action tremor			Age average (range)	M:F	Visual acuity
		Type	**Severity**	**Duration**			
To the start	**HC** (n=23)	-	-	-	42.7 (21-68)	9:14	95.7%
	OT (n=20)	DT: 15 ET: 4 WD: 1	Very mild: 2 Mild: 12 Moderate: 5 Severe: 1	24.2y	52.5 (21-78)	10:10	99.5%
	FND (n=19)	functional: 19	Very mild: 2 Mild: 8 Moderate: 8 Severe: 1	6.1	49.7 (21-75)	8:11	91.4%
	One-way ANOVA				$F(2,59)=2.17$ $p = .12$		$F(2,59)=2.93$ $p = .061$
	Chi-square goodness of fit		$\chi^2(3)= 1.47$ $p = .69$			$\chi^2(2)=0.54$ $p = .76$	
	Two-sample t-test			**$p < .0001$**			

Table 106: Participants' characteristics for the move to the start condition
With the corresponding statistical tests. DT: dystonic tremor, ET: essential tremor, WD: Wilson disease.

A 5.4 Direct versus indirect visual feedback

Explicit focus on the target with direct versus indirect visual feedback

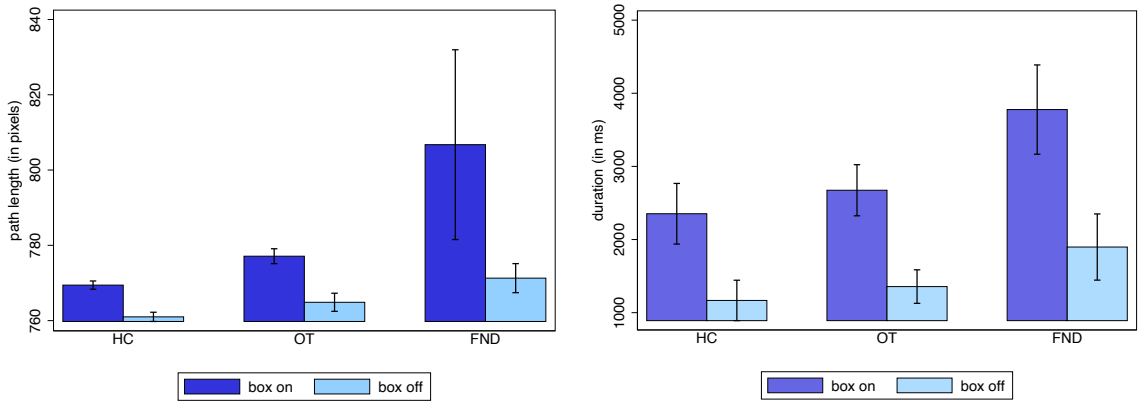


Figure 107: Path lengths of box on versus box off explicit attention to the target conditions
Path lengths with indirect (box on) and direct (box off) visual feedback for the three groups. The left figure depicts the path lengths, the right the durations. The error bars indicate the standard error of the mean.

In all three groups, the path length and durations were significantly longer with the indirect compared to the direct visual feedback (see Table 108).

Assumptions check

	Shapiro-Wilk normality test (*p*-value)			
	Path length		Duration	
	Box **on** focus on the target	Box **off** focus on the target	Box on focus on the target	Box off focus on the target
HC (n=20)	.11	.50	**.00003**	**< .0001**
OT (n=19)	**.014**	.079	**.020**	**.0024**
FND (n=17)	**< .0001**	**.014**	.051	**.00009**
Levene	***p* = .014**	***p* = .019**	***p* = .040**	*p* = .18

Table 107: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

	Box on focus on the target	Box off focus on the target	Paired t-test	Wilcoxon signed-rank test
Path length mean (*sd*) (median) in pixels				
HC (n=20)	769 (4.9) (769)	761 (5.5) (762)	$t(19) = 9.33$, $d = 2.09$ ***p< .0001***	
OT (n=19)	777 (8.6) (775)	765 (10.5) (763)		$Z = 3.78$, $r = .87$ **$p = .0002$**
FND (n=17)	807 (104.0) (780)	771 (15.9) (766)		$Z = 2.67$, $r = .65$ **$p = .0075$**
Duration mean (*sd*) (median) in ms				
HC (n=20)	2353 (1855) (1671)	1167 (1236) (860)		$Z = 3.92$, $r = .88$ **$p = .0001$**
OT (n=19)	2674 (1524) (2028)	1357 (1000) (844)		$Z = 3.82$, $r = .88$ **$p = .0001$**
FND (n=17)	3777 (2517) (2604)	1897 (1866) (1268)		$Z = 2.58$, $r = .63$ **$p = .0099$**

Table 108: Explicit focus on the target box on versus off

Explicit focus on the movement with direct versus indirect visual feedback

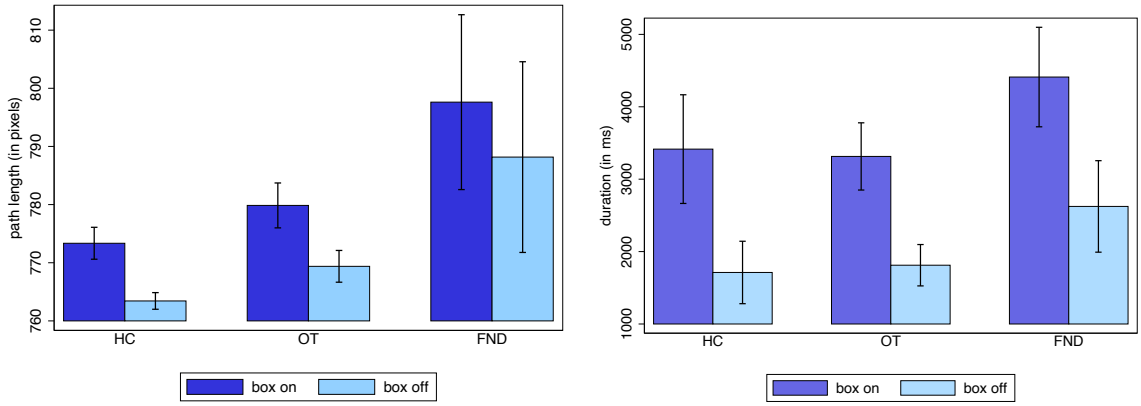


Figure 108: Path lengths of box on versus box off explicit attention to the movement conditions
Path lengths with indirect (box on) and direct (box off) visual feedback for the three groups. The left figure depicts the path lengths, the right the durations. The error bars indicate the standard error of the mean.

In all three groups, the path length and durations were significantly longer with the indirect compared to the direct visual feedback (see Table 110).

Assumptions check

	Shapiro-Wilk normality test (*p*-value)			
	Path length		Duration	
	Box **on** focus on the movement	Box **off** focus on the movement	Box **on** focus on the movement	Box **off** focus on the movement
HC (n=20)	**< .0001**	.080	**< .0001**	**< .0001**
OT (n=19)	**< .0001**	**.00070**	**.0043**	**.0041**
FND (n=17)	**< .0001**	**< .0001**	.062	**< .0001**
Levene	*p* = .056	***p* = .021**	*p* = .47	*p* = .43

Table 109: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

	Box on **Focus on the movement**	**Box off** **Focus on the movement**	**Wilcoxon** **signed-rank test**
Path length mean (*sd*) (median) in pixels			
HC (n=20)	773 (12.3) (771)	763 (6.4) (764)	$Z = 3.92$, $r = .88$ $\boldsymbol{p = .0001}$
OT (n=19)	780 (16.8) (775)	769 (11.9) (766)	$Z = 3.22$, $r = .74$ $\boldsymbol{p = .0013}$
FND (n=17)	798 (62.0) (781)	788 (67.6) (769)	$Z = 2.01$, $r = .49$ $\boldsymbol{p = .044}$
Duration mean (*sd*) (median) in ms			
HC (n=20)	3415 (3357) (2509)	1712 (1928) (1441)	$Z = 3.62$, $r = .81$ $\boldsymbol{p = .0003}$
OT (n=19)	3314 (2023) (2702)	1812 (1245) (1516)	$Z = 3.82$, $r = .88$ $\boldsymbol{p = .0001}$
FND (n=17)	4411 (2834) (3522)	2624 (2605) (1995)	$Z = 2.25$, $r = .55$ $\boldsymbol{p = .025}$

Table 110: Explicit focus on the movement box on versus off

A 5.5 Absent visual feedback versus direct visual feedback

Directly comparing the pathlengths and durations of the trajectories performed without and visual feedback and with direct visual feedback gave the following results:

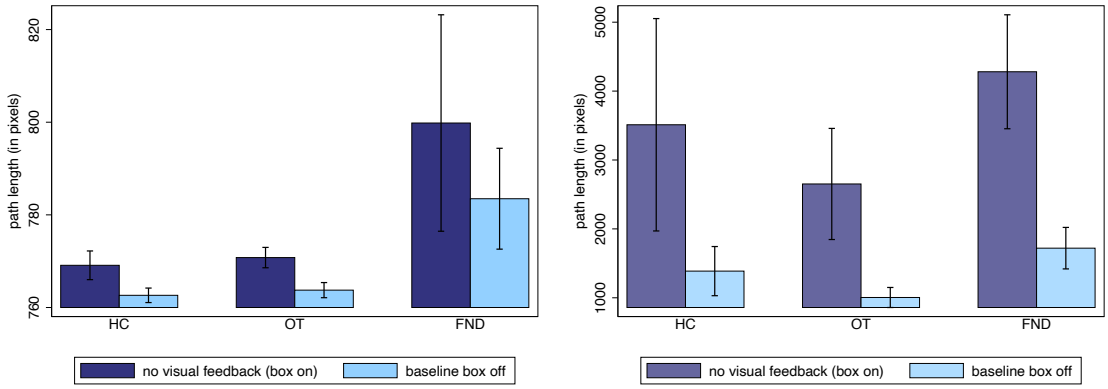


Figure 109: Absent visual feedback versus direct visual feedback
The absent visual feedback condition was performed with indirect visual feedback, the baseline condition with direct visual feedback. The left figure depicts the path lengths, the right the durations. The error bars indicate the standard error of the mean.

The path lengths were significantly shorter in both control groups, but not in the FND group. The durations were significantly prolonged in both tremor groups (Table 112).

	Shapiro-Wilk normality test (*p*-value)			
	Path length		**Duration**	
	Absent visual feedback Box on	**Baseline box off**	**Absent visual feedback Box on**	**Baseline box off**
HC (n=8)	.10	.84	**.0003**	**.002**
OT (n=12)	.22	.11	**.0004**	**.015**
FND (n=11)	**< .0001**	**.0004**	**.049**	.052
Levene	*p* = .046	***p* = .0025**	*p* = .50	*p* = .37

Table 111: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene´s test of homogeneity of variance in purple. Significant results are in bold.

	Absent visual feedback Box on	**Baseline box off**	**Paired t-test**	**Wilcoxon signed-rank test**
Path length mean (*sd*) (median) in pixels				
HC (n=8)	769 (8.8) (767)	763 (4.4) (763)	$t(7) = 2.71$, $d = 0.96$ $\mathbf{p = .030}$	
OT (n=12)	771 (7.6) (769)	764 (5.7) (765)	$t(11) = 3.78$, $d = 1.09$ $\mathbf{p = .003}$	
FND (n=11)	800 (77.5) (776)	783 (36.1) (770)		$Z = 1.33$, $r = .40$ $p = .18$
Duration mean (*sd*) (median) in ms				
HC (n=8)	3511 (4359) (1693)	1387 (1009) (1242)		$Z = 1.68$, $r = .59$ $p = .09$
OT (n=12)	2652 (2793) (1744)	1004 (504) (772)		$Z = 3.06$, $r = .88$ $\mathbf{p = .002}$
FND (n=11)	4281 (2743) (3406)	1720 (999) (1754)	$t(10) = 3.90$, $d = 1.18$ $\mathbf{p = .003}$	$Z = 2.85$, $r = .86$ $\mathbf{p = .004}$

Table 112: Absent visual feedback versus direct visual feedback

Note that the number of participants were rather small, thus caution is required in the interpretation of these results.

A 5.6 Accuracy versus explicit focus on the movement

Comparisons between focus on the accuracy of the movement versus explicit focus on the movement gave the following results:

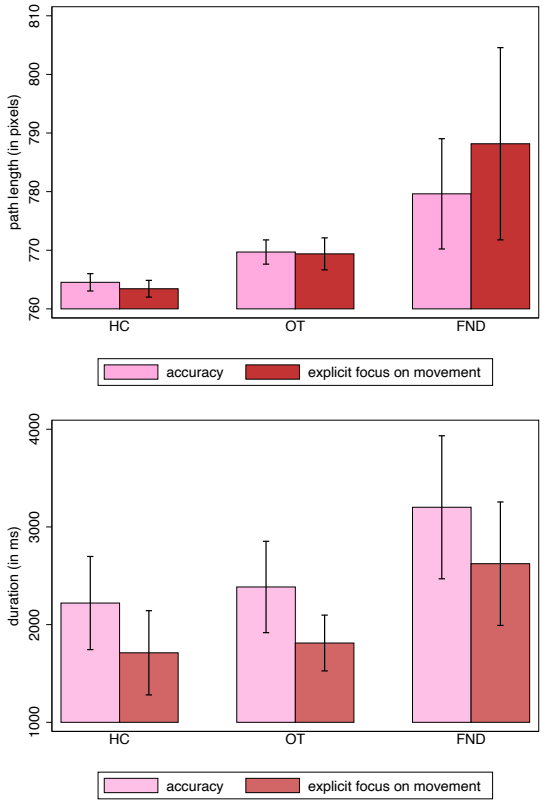


Figure 110: Explicit focus on accuracy versus explicit focus on the movement
Both conditions were performed with direct visual feedback. The left figure depicts the path lengths, the right the durations. The error bars indicate the standard error of the mean.

There was no significant difference between the path lengths. In terms of durations, the healthy controls were significantly slower in the accuracy condition and there was a trend in the same direction for both tremor groups.

	Shapiro-Wilk normality test (*p*-value)			
	Path length		**Duration**	
	Accuracy	**Explicit attention to movement**	**Accuracy**	**Explicit attention to movement**
HC (n=20)	0.25	.080	**< .0001**	**< .0001**
OT (n=19)	0.062	**.0007**	**0.00077**	**.0041**
FND (n=17)	**< .0001**	**< .0001**	**< .0001**	**< .0001**
Levene	***p* = .043**	***p* = .021**	*p* = .73	*p* = .43

Table 113: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

	Accuracy	Explicit attention to movement	Paired t-test	Wilcoxon signed-rank test
Path length mean (*sd*) (median) in pixels				
HC (n=20)	765 (6.6) (765)	763 (6.4) (764)	$t(19) = 1.49$, $d = 0.33$ $p = .15$	
OT (n=19)	770 (9.0) (767)	769 (11.9) (766)		$Z = 0.52$, $r = .12$ $p = .60$
FND (n=17)	780 (38.8) (768)	788 (67.6) (769)		$Z = -1.02$, $r = -.25$ $p = .31$
Duration mean (*sd*) (median) in ms				
HC (n=20)	2221 (2132) (1609)	1712 (1928) (1441)		$Z = 2.17$, $r = .48$ $\mathbf{p = .030}$
OT (n=19)	2385 (2037) (1863)	1812 (1245) (1516)		$Z = 1.89$, $r = .43$ $p = .0059$
FND (n=17)	3201 (3019) (2168)	2624 (2605) (1995)		$Z = 1.87$, $r = .45$ $p = .0062$

Table 114: Focus on accuracy versus explicit attentional focus on the movement

A 5.7 Attention to the target versus the movement

Indirect visual feedback

Explicit attention to the target versus the movement (indirect visual feedback)

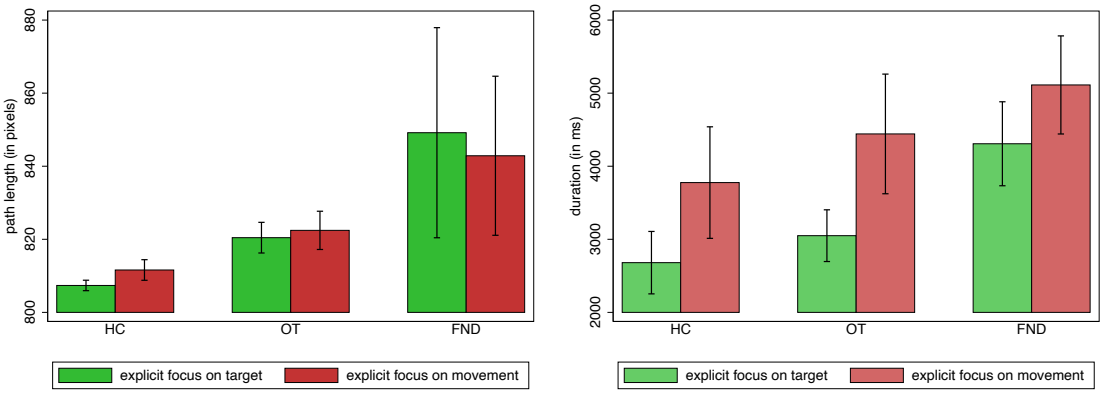


Figure 111: Explicit attentional focus on the target versus the movement (indirect visual feedback)

Directly comparing the path lengths in the explicit attention to the target versus the movement conditions showed no significant difference in the path lengths in any of the groups. The durations were significantly shorter with explicit attention on the target in both control groups. (Table 116)

	Shapiro-Wilk normality test (*p*-value)			
	Path length		**Duration**	
	Explicit attention to target	**Explicit attention to movement**	**Explicit attention to target**	**Explicit attention To movement**
HC (n=20)	**.021**	**.0002**	**< .0001**	**< .0001**
OT (n=21)	**.001**	**< .0001**	**.003**	**< .0001**
FND (n=19)	**< .0001**	**< .0001**	.11	.088
Levene	***p* = .032**	*p* = .059	*p* = .094	*p* = .91

Table 115: Shapiro-Wilk normality test and Levene's test of homogeneity of variance
The *p*-values of the Shapiro-Wilk normality test are highlighted in blue, those of Levene's test of homogeneity of variance in purple. Significant results are in bold.

	Explicit attention to target	Explicit attention to movement	Paired t-test	Wilcoxon signed-rank test
Path length mean (*sd*) (median) in pixels				
HC (n=20)	807 (6.4) (806)	812 (12.6) (807)		*Z* = -1.31, *r* = -.29 *p* = .19
OT (n=21)	820 (19.2) (817)	822 (24.0) (816)		*Z* = -0.68, *r* = -.15 *p* = .50
FND (n=19)	849 (125.3) (813)	843 (94.9) (818)		*Z* = 0.28, *r* = .06 *p* = .78
Duration mean (*sd*) (median) in ms				
HC (n=20)	2680 (1910) (1969)	3776 (3414) (2937)		*Z* = -3.10, *r* = -.69 ***p* = .002**
OT (n=21)	3050 (1622) (2447)	4442 (3751) (2971)		*Z* = -2.80, *r* = -.61 ***p* = .005**
FND (n=19)	4307 (2504) (4018)	5112 (2926) (4294)	*t*(18)=-1.76, *d =-0.40* *p* = .096	

Table 116: Explicit attention to the target versus the movement (indirect visual feedback)

A 6 Patients' perception

A 6.1 Masters' movement specific reinvestment scale for all subjects

	Healthy control (n=57) (*sd*)	organic movement disorder (n=41) (*sd*)	functional movement disorder (n=52) (*sd*)	One-way ANOVA	
Overall score	21.9 (11.6)	36.6 (13.6)	36.0 (12.0)	$F(2,147) = 23.97$ $\eta^2 = .25$	$p < .0001$
Conscious motor processing sub-score	11.8 (6.8)	18.8 (7.1)	19.0 (6.9)	$F(2,147) = 18.96$ $\eta^2 = .21$	$p < .0001$
I rarely forget the times when my movements have failed me, however slight the failure.	2.5 (2.0)	3.5 (1.8)	3.6 (1.9)	$F(2,147) = 5.11$ $\eta^2 = .065$	$p = .007$
I am always trying to figure out why my actions failed.	2.4 (1.9)	3.1 (2.0)	3.7 (1.8)	$F(2,147) = 7.06$ $\eta^2 = .088$	$p = .001$
I reflect about my movement a lot.	2.1 (1.6)	4.1 (1.7)	3.9 (1.8)	$F(2,147) = 23.73$ $\eta^2 = .24$	$p< .0001$
I am always trying to think about my movements when I carry them out.	2.2 (1.7)	3.8 (1.8)	3.9 (2.0)	$F(2,147) = 14.61$ $\eta^2 = .17$	$p < .0001$
I am aware of the way my mind and body works when I am carrying out a movement.	2.7 (1.8)	4.3 (1.8)	3.9 (1.8)	$F(2,147) = 11.31$ $\eta^2 = .13$	$p < .0001$
Movement self-consciousness sub-score	10.1 (6.0)	18.0 (7.2)	16.9 (6.8)	$F(2,147) = 21.52$ $\eta^2 = .23$	$p < .0001$
I am self-conscious about the way I look when I am moving.	2.5 (1.7)	4.0 (1.9)	4.2 (1.8)	$F(2,147) = 14.95$ $\eta^2 = .17$	$p = .0001$
I sometimes have the feeling that I am watching myself move.	1.6 (1.2)	3.4 (1.9)	2.9 (1.9)	$F(2,147) = 16.08$ $\eta^2 = .18$	$p < .0001$
I am concerned about my style of moving.	1.8 (1.4)	3.7 (1.8)	3.7 (1.7)	$F(2,147) = 24.34$ $\eta^2 = .25$	$p < .0001$
If I see my reflection in a shop window, I will examine my movements.	2.3 (1.6)	2.6 (1.7)	2.5 (1.8)	$F(2,147) = 0.57$ $\eta^2 = .008$	$p = .57$
I am concerned about what people think about me when I am moving.	1.9 (1.4)	4.1 (1.8)	3.7 (1.9)	$F(2,147) = 24.33$ $\eta^2 = .25$	$p < .0001$

Table 117: Master's movement specific reinvestment scale for all subjects
Overall score, sub-scores for the two subscales, and scores for each individual question, together with the respective one-way ANOVA. Eta squared (η^2) gives the effect size.

Concerning the assumptions of the one-way ANOVA, Levene's test of equality of variance was not significant for the overall score (p = .61), nor for the conscious motor processing sub-score (p = .89), nor the movement self-consciousness sub-score (p = .42). The healthy control group was not normally distributed, but both tremor groups could be assumed to be.

A 6.2 Attention to good outcome

	Worse	**Same or it depends**	**Better**
HC (n=37)	46.0%	16.2%	37.8%
OT (n=37)	70.3%	8.1%	21.6%
FND (n=40)	58.8%	15.8%	25.4%
Chi square goodness of fit test	χ^2 (4) =7.85		
	p =.097		

Table 118: Responses to the question: "When you try hard to make a movement perfect, do you think it turns out better or worse than if you just did it without much thought?"
Patients with any type of functional or organic movement disorder are included.

A 7 Intentional binding data

	baseline IB - pure interval estimate	IB with attentional manipulation on target - baseline IB	IB with attentional manipulation on movement - baseline IB
HC (n=18)	49.7	-27.0	-48.3
OT (n=8)	6.9	-36.5	-58.6
FND (n=8)	-18.2	-74.6	-90.8

Table 119: Absolute differences for the intentional binding conditions
Group averages for the absolute differences in the interval estimates of the different conditions compared to the pure interval estimate in the first comparison and compared to the baseline intentional binding condition for the other two comparisons. Note that the baseline intentional binding task does not induce intentional binding (no negative figures) in the two control groups (1st column), so the other comparisons become meaningless. IB: intentional binding.

	Pure interval estimate (no movement) (group average)			**Baseline intentional binding (with movement but without attentional manipulation)** (group average)		
	intercept	slope	R2	intercept	slope	R2
HC (n=18)	-75.5	0.88	0.64	28.5	0.79	0.60
OT (n=8)	5.9	0.66	0.47	30.2	0.63	0.54
FND (n=8)	134.0	0.67	0.42	50.0	0.77	0.57

Table 120: Linear regression analysis of pure interval estimate and baseline interval estimate
The similar slopes between the two conditions in each group mean that the intercepts are interpretable and the intercept increases in the baseline intentional binding condition compared to the pure interval estimate condition, in both control groups, indicating that the task did not induce intentional binding. Abbreviations: R2: squared regression coefficient.

A 8 Agency with subliminal & supraliminal priming

A 8.1 Instructions

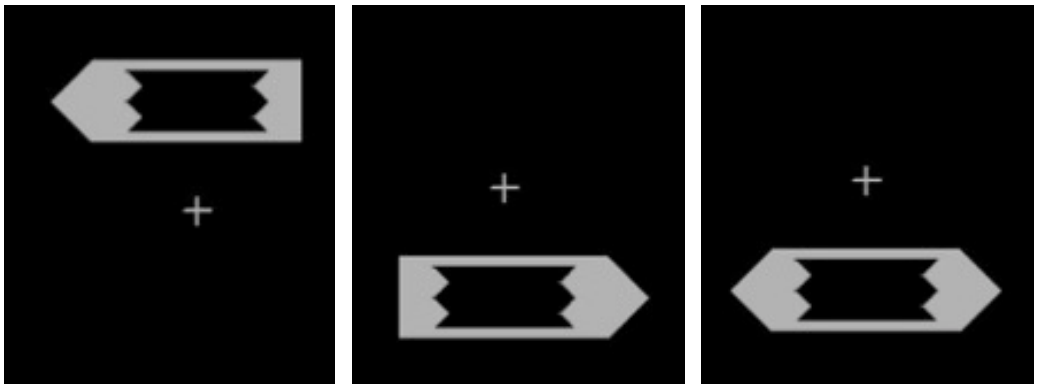
A 8.1.1 Instructions – subliminal prime

A 8.1.1.1 1st priming and agency experiment

Sense of control

This is an experiment investigating perceived sense of control (feelings of causation).

You will be shown a large arrow on the screen pointing either to the left or to the right, or in both directions. The arrows may appear above or below the fixation point (+):



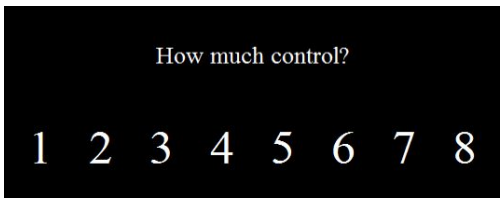
When the large arrow points to the left, press the left pointing arrow (←) with your left hand, when it points to the right, press the right pointing arrow (→) with your right hand. Do so as quickly as possible.
If you see a double-arrow, you have to choose on the spot whether to use your left or right hand. Don´t follow a fixed pattern, but try to decide anew each time you see the double-arrow.

If you pressed the wrong key or responded too slowly, you will see a large X. Otherwise your keypress makes a coloured circle appear in the middle of the screen, e.g.:

We would like you to indicate how much control you felt you had over the appearance of the coloured circle, on a scale from 1 to 8

1: no control at all: “I had no control over the colour appearing on the screen”

8: complete control: “I had total control over the colour appearing on the screen”.



No control complete control

There are different colours and the delay before the coloured circle appears will also vary. In order to decide how much control you had over its appearance, think about the relationship between what key you pressed and what *colour* you see and *when* it appeared.

The experiment contains 7 blocks. The first block is for practice and takes about two minutes. The other 6 blocks are experimental blocks and each takes about five minutes. After each block there will be a short break.

A 8.1.1.2 2nd priming and agency experiment

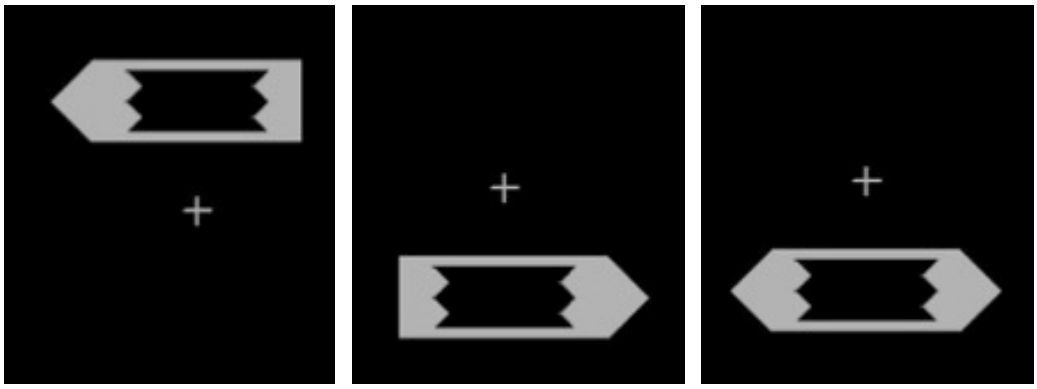
If the supraliminal prime experiment has already been done, the instructions are simplified:

Sense of control

This experiment is the same as the previous one, except that **you will no longer be shown the little arrow beforehand.**

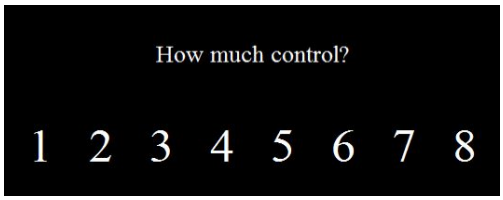
Also note that the colours you will see in this experiment, have nothing to do with the colour combinations in the previous one.

The rest of the experiment is the same:



When you see the large arrow on the screen respond as quickly as possible by pressing the left or right arrow key. When the arrow points in both directions, choose on the spot which arrow to press. Don´t follow a fixed pattern, but decide anew each time you see the double-arrow.

After the coloured circle has been shown, indicate how much control you feel you had over its appearance.



No control complete control

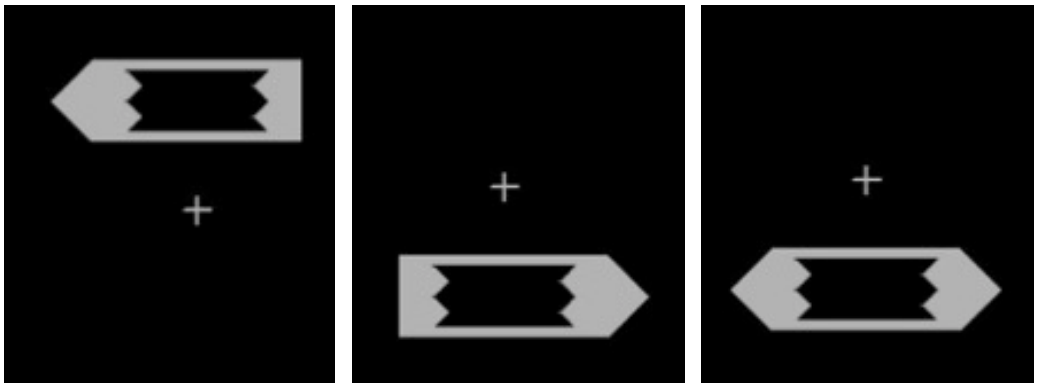
A 8.1.2 Instructions – supraliminal prime

A 8.1.2.1 1st priming and agency experiment

Sense of control

This is an experiment investigating perceived sense of control (feelings of causation).

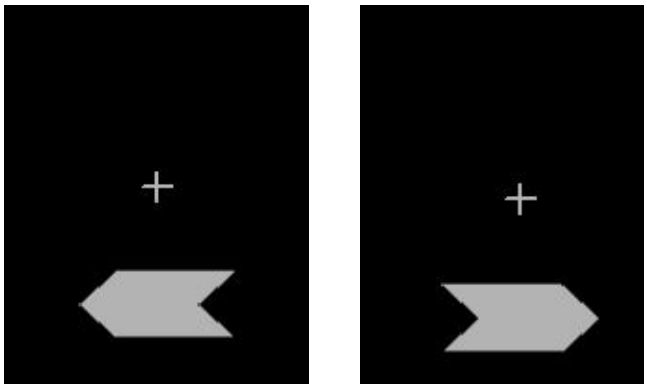
You will be shown a large arrow on the screen pointing either to the left or to the right, or in both directions. The arrows may appear above or below the fixation point (+):



When the large arrow points to the left, press the left pointing arrow (←) with your left hand, when it points to the right, press the right pointing arrow (→) with your right hand. Do so as quickly as possible.

If you see a double-arrow, you have to choose on the spot whether to use your left or right hand. Don´t follow a fixed pattern, but try to decide anew each time you see the double-arrow.

Just before the large arrow, you will see a small arrow pointing either to the left or to the right. You can ignore the small arrow.

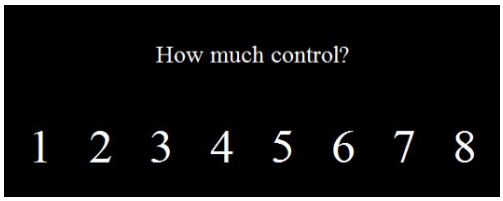


If you pressed the wrong key or responded too slowly, you will see a large X.
Otherwise your keypress makes a coloured circle appear in the middle of the screen, e.g.:

We would like you to indicate how much control you felt you had over the appearance of the coloured circle, on a scale from 1 to 8

1: no control at all: “I had no control over the colour appearing on the screen”

8: complete control: “I had total control over the colour appearing on the screen”.



No control complete control

There are different colours and the delay before the coloured circle appears will also vary. In order to decide how much control you had over its appearance, think about the relationship between what key you pressed and what *colour* you see and *when* it appeared.

The experiment contains 7 blocks. The first block is for practice and takes about two minutes. The other 6 blocks are experimental blocks and each takes about five minutes. After each block there will be a short break.

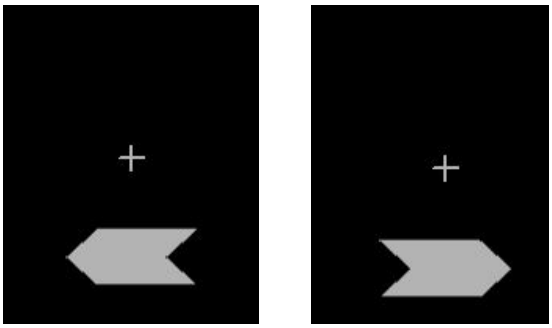
A 8.1.2.2 2nd priming and agency experiment

If the subliminal prime experiment has already been done, the instructions are simplified:

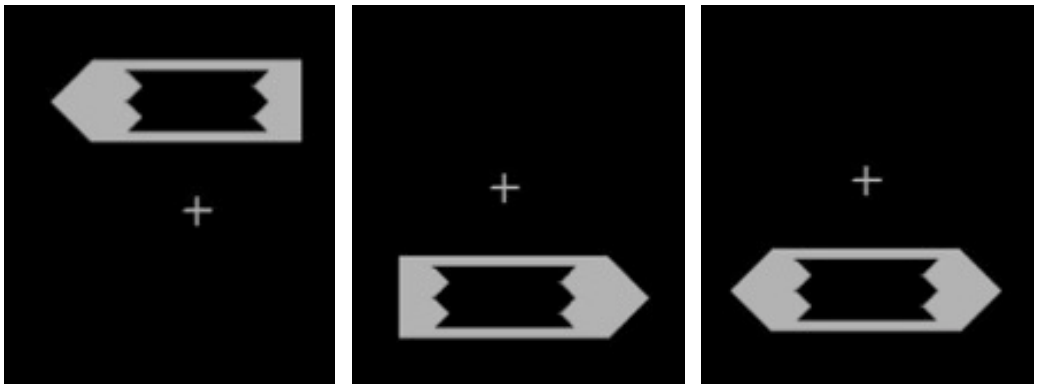
Sense of control

This experiment is the same as the previous one, except that **you will see the small arrow.**

So first you will see a small arrow pointing either to the left or to the right. You can ignore it.



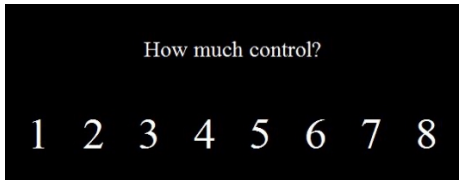
The rest of the experiment is the same:



When you see the large arrow on the screen respond as quickly as possible by pressing the left or right arrow key. When the arrow points in both directions, choose on the spot which arrow to press. Don´t follow a fixed pattern, but decide anew each time you see the double-arrow.

Note that the colours you will see in this experiment, **have nothing to do with the colour combinations in the previous one.**

After the coloured circle has been shown, indicate how much control you feel you had over its appearance.



No control complete control

A 8.2 Stimuli

A 8.2.1 Coloured circles

Two colours were randomly assigned for left compatible responses, two to right compatible responses, two to left incompatible responses and two to right incompatible responses.

Compatibility means the subject's response was in the same direction as the prime arrow.

- Compatible if prime and response are the same
  - Fixed choice: if prime and mask are compatible and the correct key is pressed
  - free choice: response being the same as the prime direction
- Incompatible if prime and response are not the same
  - Fixed choice: prime and mask are incompatible and subject pressed the correct key in response to the mask
  - Free choice: response being the opposite of prime direction

Remember that if wrong key was pressed with regards to the mask, a large white X appeared and the trial was discarded and repeated at the end.

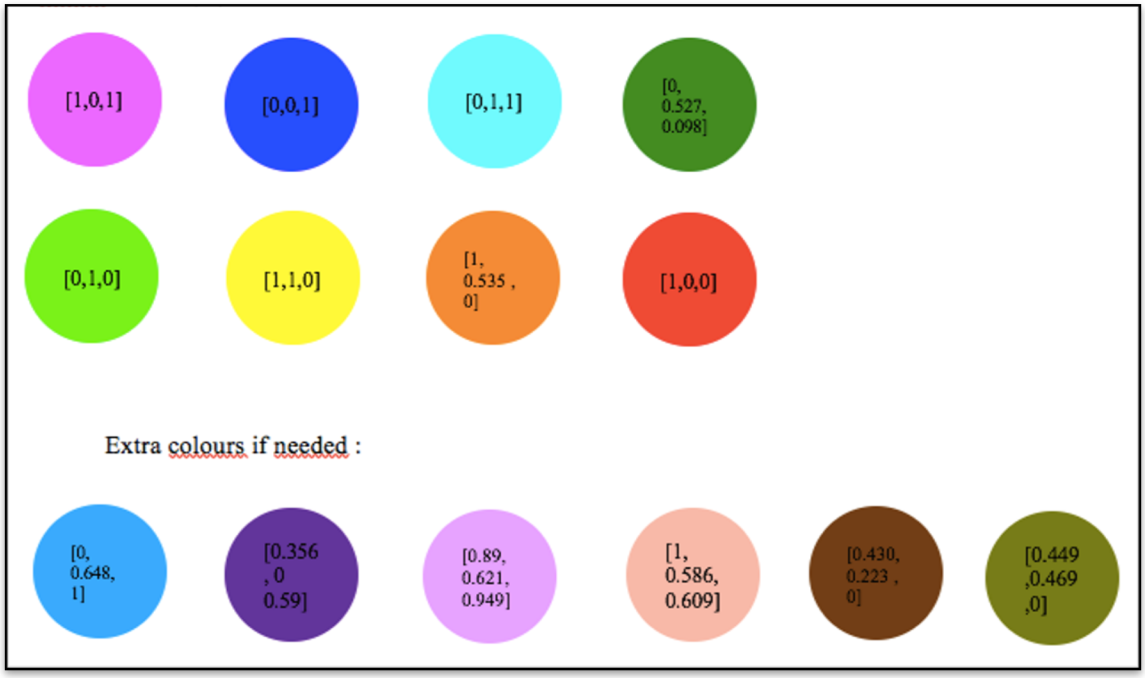


Figure 112: Coloured circles
The eight colours used for the coloured circles (effects), with their colour code ([Red, Green, Blue]) from 0-1. Colours that were not perceived as distinctly different could be exchanged with any of the additional colours below.

A 8.2.2 Stimuli sizes

	Visual angle (in degrees)
Prime	
• Prime height	0.8º
• Prime length	1.86º
Mask	
• Mask height	1.09º
• Unidirectional mask length	3.26º
• Bidirectional mask length	3.48º
Prime and mask location above or below fixation	1.38º
Fixation cross (+) and cue (*)	
• Line length	0.34º
• Line thickness	0.03º
Coloured circles	
• Diameter	1.86º

Table 121: Priming study stimuli sizes
The sizes are given in visual angle. The viewing distance was 65cm. Note that the middle rectangular part of the bidirectional masks was a bit shorter than that of the unidirectional masks, so that the total length and total surface area remained the same as the unidirectional masks and the prime

A 8.2.3 Display durations

Initial fixation cross	1500ms
Prime Subliminal Supraliminal	 16.6ms (1 frame) 200ms
Fixation cross between prime and mask with subliminal prime with supraliminal prime	 33ms (2 frames) 200ms
Mask/target	250ms
Maximum response time	1500ms
Interval between response and colour circle	100, 400 or 700ms (random order)
Colour circle	800ms
Blank screen after colour circle	1000ms
Maximum response time for agency rating	indefinitely

Table 122: Priming study display durations

A 8.3 Additional results

A 8.3.1 Subliminal priming agency rating in free choice condition only

A 8.3.1.1 Assumptions check

For the mixed ANOVA with group as between factor and congruence as within-subject factor, all combinations of these two factors were normally distributed (Shapiro-Wilk for prime-congruent responses in HC p = .86, in FND p = .095, and for prime-incongruent responses HC: 0.80, FND 0.17). Levene´s test for homogeneity of variance across the groups was insignificant for both the incongruent (p = .096) and the congruent (p = .59) responses. The raw data thus met the assumptions of the mixed model ANOVA and no normalisation was required.

A 8.3.1.2 Mixed model ANOVA

A mixed model ANOVA with group as between-subject factor and congruence as within-subject factor, for the free choice condition only, did not give a significant main effect of congruence (GG $F(1,36) = 0.62$, $\eta_p^2 = .017$, $p = .44$) nor of the interaction group x congruence (GG $F(1,36) = 0.01$, $\eta_p^2 = .0003$, $p = .92$).

A 9 Placebo response

A 9.1 Linear Mixed Effects model

A 9.1.1 Model

A linear mixed effects analysis approach was used to analyse the data.

The pain rating was modelled as a function of the group (FND vs HC), the site (placebo cream site vs control cream site), the condition (baseline, post-cream, post-conditioning, post-disclosure), the repetition and the subject. All these factors were modelled as fixed effects, with the exception of the subject factor, which was modelled as a random effect.

The main effect of repetition was significant in every comparison mentioned below and will therefore not be mentioned each time.

A 9.1.2 Comparisons

The following comparisons were performed:

Baseline ratings

The placebo site baseline rating was significantly larger than the control site baseline rating (p = .015), but there was no difference between the two groups. The average difference was 0.12 on a scale from 0 to 10, which was not clinically significant.

Post-cream versus baseline

There was a significant interaction between site and condition, indicating that the pain rating for the two conditions significantly differed at the placebo and control sites. Importantly, the **significant interaction between group, site and condition**, indicated that the site condition interaction was different in the two groups (***p* = .0041**).

Looking at the raw data (Figure 74 and Figure 75) made it clear that although both groups demonstrate a placebo effect on the placebo site, it was more marked in the healthy controls (HC decrease in pain rating 0.590, FND decrease in pain rating 0.397).

Post-conditioning versus post-cream

There was no significant decrease in the pain rating following the conditioning stimulus compared to following the administration of the placebo cream (p = .94). There was also no significant group x site x condition interaction (p = .48)

Post-conditioning versus baseline

This comparison looks at the sum of the overall placebo and conditioning effect.

The post conditioning versus baseline comparison showed a significant interaction of site x condition. Importantly there was **a significant interaction effect of group x site x condition (*p* = .042)**. Looking at the raw data showed that there was a larger overall placebo effect in the healthy controls than there was in the FND group.

Post-disclosure versus post-conditioning

There was a significant interaction between site and condition (p = .0138), indicating that difference in pain rating between the two conditions varied according to the two sites. The raw data (Figure 74), showed that on the placebo site, the pain rating increased post disclosure. There was no significant difference between the two groups (interaction of group x site x condition p = .6073).

Baseline versus post-disclosure: open label placebo effect post experience and disclosure of deceptive placebo and conditioning

There was a significant interaction of site x condition (p = .0016), indicating that there was a different pain rating in the two conditions at the different sites. This excludes the decreased pain rating being simply due to adaptation to the painful stimulus over time. There was no significant difference of that effect between the two groups (interaction group x site x condition p = .0946).

This effect can be interpreted as the open-label placebo effect following the exposure to and disclosure of a deceptive placebo and a conditioning effect.

A 9.1.3 Considerations

The issue of this linear mixed effects model is that the variances of the residuals were dissimilar – meaning the assumptions were not met (Figure 113). It is unclear in how far the linear mixed effects model is robust to this violation of its assumptions.

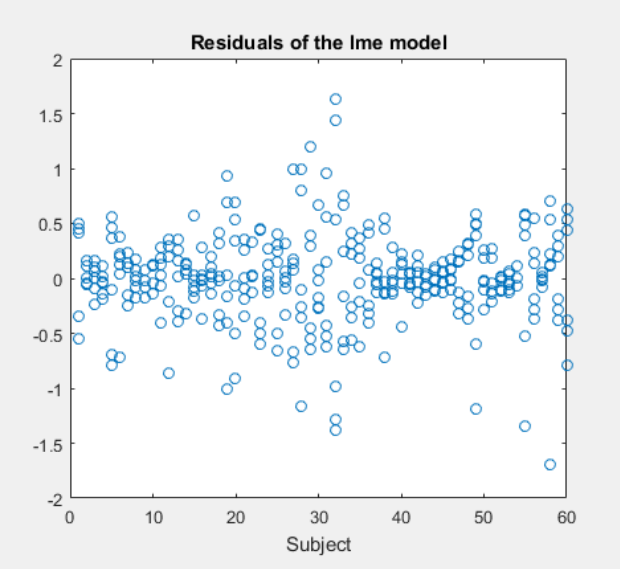


Figure 113: Residuals of the linear mixed effects model

The variance of the residuals for each subject. Subjects 1 to 30 are healthy controls. Subjects 31 to 60 are FND patients.

A 10 Placebo survey

A 10.1 Patients' and healthy controls' questionnaire

Questionnaire on the use of placebo in clinical practice

We would like to ask you about your thoughts on whether or not placebo treatments should be used in medicine. Please note that we are simply interested in your opinion and are not encouraging their use. This questionnaire is entirely voluntary and anonymous.

Before answering the questions, please read the following carefully:

Definition
Placebo can be defined in many ways. In this questionnaire we are using the word placebo to describe a situation when someone is led to believe that the treatment they are receiving is a standard, active treatment, like a medication pill, although in reality it has nothing active in it. This type of placebo is called "deceptive placebo".

The "placebo effect" is when medical problems get better as a result of taking a placebo treatment. This is a genuine effect and is seen in a wide range of conditions. A placebo effect does not occur because of the actual substance itself, as it is inactive.

Deceptive placebo is not allowed in many healthcare systems. This is why this issue is controversial and why we are asking your opinion.

Important note
When answering the questions about placebo treatments, please assume the following:

- The doctor has done everything they can and there is no better standard treatment available
- The only reason the placebo treatment is given is to make the person's symptoms better through the placebo effect
- All the cases that follow refer to real life scenarios and not to research studies

Questions
Please answer each question by ticking **one** of the boxes. If you wish, you can write comments in the space below each question. Please try to avoid answering "I don´t know".

1) What are your initial thoughts? Do you think doctors should use deceptive placebo treatments if they think their patient could get a beneficial placebo effect from it?

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

2) Do you think a placebo treatment could improve your symptoms? (If you do not currently suffer from a medical condition, think about a medical problem you have experienced in the past)

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

3) Considering potential risks of deceptive placebo treatment, where the patient does not know that the treatment is a placebo:

a) If doctors used deceptive placebo treatments, patients would lose trust in doctors and medicine.

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

b) By receiving deceptive placebo treatments patients might become over reliant on medicines and interventions, rather than learn to cope and manage their symptoms themselves.

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

4) Placebos work best when the patient does not know that the treatment they are receiving is a placebo (deceptive placebo). However, placebo can also work when the patient is told right from the start that the treatment is a placebo ("open-label placebo").

a) Placebo treatments should only be given in an open way. Patients should be told very clearly from the beginning if a treatment is a placebo, even if that meant it wouldn´t work as well.

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

b) If a doctor were to give a placebo, they should *not* tell the patient that it is a placebo so that it is as effective as possible, even if that meant the doctor not telling the full truth.

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

c) It is acceptable for a doctor to give a placebo without telling the patient that it is a placebo and instead to remain vague and say: “This treatment sometimes works really well against the type of problems you have, so let’s give it a try.”

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

d) I think that open-label placebo treatments (telling the patient that it is a placebo and that placebos are powerful) work just as well as deceptive placebo treatments (not telling the patient that it is a placebo).

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

e) Imagine your doctor giving you a placebo treatment for a medical problem. When would you want your doctor to tell you that the treatment is a placebo? (select all that apply)

- ☐ Never
- ☐ Before starting (open-label placebo)
- ☐ If it has worked and I am no longer taking it
- ☐ If it is working and I am still taking it
- ☐ If it hasn´t worked
- ☐ Irrelevant - I would never want my doctor to give me a placebo, neither open-label nor deceptive
- ☐ Other (please explain)

  _____

5) Although nearly any condition can be associated with a placebo effect, only some conditions can show it to an extreme degree. A placebo could therefore be used to help make a diagnosis of these types of conditions.
It is acceptable to use a deceptive placebo as a diagnostic tool in such cases.

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

6) Some disabling conditions sometimes show strong placebo responses, with full recovery. In such cases, if standard treatments are unsuccessful, a doctor should attempt the following:

a) **deceptive** placebo

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

b) **open-label** placebo

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

7) An active (standard) drug will work better if it is given by a doctor the patient trusts fully, than if it is given by a doctor the patient trusts less.

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

8) If a patient fully trusts a doctor, and that doctor tells the patient that their medical problem can improve or disappear if the patient believes it will, then this would work just as well as a placebo treatment.

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

9) The most important factors for me to fully trust a doctor are: (Choose **5 answers**)

- ☐ give me enough time during my appointment
- ☐ listen to me
- ☐ explain the diagnosis and the treatment
- ☐ examine me
- ☐ reassure me
- ☐ be kind
- ☐ look at me as a whole person and not a single medical problem
- ☐ perform many tests (investigations)
- ☐ use modern, specialised machines
- ☐ use the newest drugs
- ☐ use well established drugs
- ☐ work in a famous, renowned hospital
- ☐ be a famous doctor
- ☐ be a famous researcher
- ☐ prescribe what I want even if they do not think it is a good treatment
- ☐ other patients telling me he or she is a good doctor
- ☐ having known the doctor for many years
- ☐ I don´t know
- ☐ Other (please explain)

_____

10) A 40-year-old man cannot move his legs and has been wheelchair-bound for 4 years despite many different treatments. All tests are normal and specific features on examination make the doctors diagnose a functional neurological disorder. This type of disorder is real and common. It may improve or persist.

a) The doctor should give him a **deceptive** placebo drug

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

b) The doctor should give him an **open-label** placebo drug

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

11) Now that you have answered some more questions, we would like to ask you the same question as at the beginning: Do you think doctors should use deceptive placebo treatments if they think their patient could get a beneficial placebo effect from it? (Please don´t go back and change your initial answer)

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

12) A placebo pill (select all that apply)

- ☐ is an inactive treatment that never improves health issues
- ☐ is an inactive treatment that can improve health issues
- ☐ works because of the substance it contains
- ☐ works because patients believe it will improve their health issues

Please use the space provided below if you wish to make any further, general comments.

……

……

……

Please provide the following information about yourself.

Age range: ☐ 18-30 years old ☐ 51-60 years old
☐ 31-40 years old ☐ 61-70 years old
☐ 41-50 years old ☐ > 71 years old

Gender: ☐ male ☐ female ☐ prefer not to say

Which diagnosis (condition) do you have or have had in the past? (tick all that apply)

☐ Neurological conditions

- ☐ Functional neurological disorder
  - ☐ Functional movement disorder (e.g. functional tremor, functional dystonia, functional weakness, functional gait disorder)
  - ☐ Non-epileptic attack disorder
  - ☐ Other functional neurological disorder
    Specify (optional)_____
- ☐ Parkinson's Disease
- ☐ Dystonia
- ☐ Tremor
- ☐ Tics
- ☐ Other movement disorder
  Specify (optional)_____
- ☐ Migraine
- ☐ Multiple sclerosis
- ☐ Epilepsy
- ☐ Other neurological condition
  Specify (optional)_____

☐ Other medical condition (non-neurological)
Specify (optional)_____

☐ Healthy volunteer (no medical condition at all)

☐ If you are unsure, please write your symptoms or diagnosis here:

_____

Thank you very much for your participation.

For further information: Dr Anne-Catherine Huys (Association of British Neurologists fellowship project: The pathophysiology of functional movement disorders) Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, 33 Queen Square, floor 6, London, WC1N 3BG. Other investigators on this study: Prof Kailash Bhatia (Chief investigator, same department) and Prof Mark Edwards (St George's University and St George's Hospital).

A 10.2 Healthcare professionals' questionnaire

Questionnaire on the use of placebo in clinical practice

(healthcare professionals)

We would like to know your opinion on the use of placebo treatments in medicine and on your current practice. Please note that we are simply interested in your opinion and are not encouraging their use. This questionnaire is entirely voluntary and anonymous.

Since an equivalent questionnaire is administered to patients, lay language is used.

Before answering the questions, please read the following carefully:

Definition
Placebo can be defined in many ways. In this questionnaire we are using the word placebo to describe a situation when someone is led to believe that the treatment they are receiving is a standard, active treatment, like a medication pill, although in reality it has nothing active in it. This type of placebo is called "deceptive placebo".

The "placebo effect" is when medical problems get better as a result of taking a placebo treatment. This is a genuine effect and is seen in a wide range of conditions. A placebo effect does not occur because of the actual substance itself, as it is inactive.

Deceptive placebo is not allowed in many healthcare systems. This is why this issue is controversial and why we are asking your opinion.

Please answer these questions from your personal viewpoint and not from a medico-legal standpoint.

Important note

When answering the questions about placebo treatments, please assume the following:

- The doctor has done everything they can and there is no better standard treatment available
- The only reason the placebo treatment is given is to make the person's symptoms better through the placebo effect
- All the cases that follow refer to patients and not to research studies

Questions
Please answer each question by ticking **one** of the boxes. If you wish, you can write comments in the space below each question. Please try to avoid answering "I don´t know".

1) What are your initial thoughts? Do you think doctors should use deceptive placebo treatments if they think their patient could get a beneficial placebo effect from it?

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

2) In what percentage of patients do you think placebo treatments would lead to clinical benefit with improved measures of symptoms or quality of life?

a) in purely **organic** symptoms

- ☐ 0%
- ☐ 10%
- ☐ 20%
- ☐ 30%
- ☐ 40%
- ☐ 50%
- ☐ 60%
- ☐ 70%
- ☐ 80%
- ☐ 90%
- ☐ 100%

b) in purely **functional** symptoms

- ☐ 0%
- ☐ 10%
- ☐ 20%
- ☐ 30%
- ☐ 40%
- ☐ 50%
- ☐ 60%
- ☐ 70%
- ☐ 80%
- ☐ 90%
- ☐ 100%

3) Considering potential risks of deceptive placebo treatment, where the patient does not know that the treatment is a placebo:

c) If doctors used deceptive placebo treatments, patients would lose trust in doctors and medicine

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

d) By receiving deceptive placebo treatments patients might become over reliant on medicines and interventions, rather than learn to cope and manage their symptoms themselves.

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

4) Placebos work best when the patient does not know that the treatment they are receiving is a placebo (deceptive placebo). However, placebo can also work when the patient is told right from the start that the treatment is a placebo ("open-label placebo").

a) Placebo treatments should only be given in an open way. Patients should be told very clearly from the beginning if a treatment is a placebo, even if that meant it wouldn´t work as well.

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

b) If a doctor were to give a placebo, they should *not* tell the patient that it is a placebo so that it is as effective as possible, even if that meant the doctor not telling the full truth.

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

e) It is acceptable for a doctor to give a placebo without telling the patient that it is a placebo and instead to remain vague and say: "This treatment sometimes works really well against the type of problems you have, so let's give it a try."

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

f) I think that open-label placebo treatments (telling the patient that it is a placebo and that placebos are powerful) work just as well as deceptive placebo treatments (not telling the patient that it is a placebo).

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

5) Although nearly any condition can be associated with a placebo effect, only some conditions can show it to an extreme degree. A placebo could therefore be used to help make a diagnosis of these types of conditions.
It is acceptable to use a deceptive placebo as a diagnostic tool in such cases.

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

6) Some disabling conditions sometimes show strong placebo responses, with full recovery. In such cases, if standard treatments are unsuccessful, a doctor should attempt the following:

a) **deceptive** placebo

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

b) **open-label** placebo

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

7) An active (standard) drug will work better if it is given by a doctor the patient trusts fully, than if it is given by a doctor the patient trusts less.

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

8) If a patient fully trusts a doctor, and that doctor tells the patient that their medical problem can improve or disappear if the patient believes it will, then this would work just as well as a placebo treatment.

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

9) The most important factors for a patient to fully trust a doctor are: (choose **5 answers**)

- ☐ give enough time during the appointment
- ☐ listen to the patient
- ☐ explain the diagnosis and the treatment
- ☐ examine the patient
- ☐ reassure the patient
- ☐ be empathetic
- ☐ look at the patient as a whole person and not as a single medical problem
- ☐ perform many tests (investigations)
- ☐ use modern, specialised machines
- ☐ use the newest drugs
- ☐ use well established drugs
- ☐ work in a famous, renowned hospital
- ☐ be a famous doctor
- ☐ be a famous researcher
- ☐ prescribe what the patient wants even if the doctor does not think it is a good treatment
- ☐ other patients telling them that the person is a good doctor
- ☐ having known the doctor for many years
- ☐ I don´t know
- ☐ Other (please explain)

  _____

10) A 40-year-old man cannot move his legs and has been wheelchair-bound for 4 years despite many different treatments. All tests are normal and specific features on examination make the doctors diagnose a functional neurological disorder. This type of disorder is real and common. It may improve or persist.

c) The doctor should give him a **deceptive** placebo drug

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

d) The doctor should give him an **open-label** placebo drug

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

11) Now that you have answered some more questions, we would like to ask you the same question as at the beginning: Do you think doctors should use deceptive placebo treatments if they think their patient could get a beneficial placebo effect from it? (Please don´t go back and change your initial answer)

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

12) A placebo pill (select all that apply)

- ☐ is an inactive treatment that never improves health issues
- ☐ is an inactive treatment that can improve health issues
- ☐ works because of the substance it contains
- ☐ works because patients believe it will improve their health issues

13) Please tick the box corresponding to your approximate use in clinical practice of deceptive (question a) and open-label placebo (question b):

(Examples of deceptive placebo are:

- telling the patient that it is a specific treatment, when it is in fact just a placebo
- giving a medication which has no effect in that specific condition, other than through a placebo effect
- giving an active treatment at an excessively low dose, so that there is no rationale for it to have any effect other than through a placebo effect

Open label placebo implies giving the patient a treatment, while explicitly telling the patient that the treatment is a placebo, that it contains no active ingredient; or that the active ingredient it contains is useless for their condition and that the effect will therefore be a pure placebo effect. This can be accompanied by positive suggestion, but it is not positive suggestion alone.)

a) **deceptive** placebos	b) **Open-label** placebos
☐ Never	☐ Never
☐ Once	☐ Once
☐ 2-5 times	☐ 2-5 times
☐ 5-10 times	☐ 5-10 times
☐ Once a year	☐ Once a year
☐ Once a month	☐ Once a month
☐ Once a week	☐ Once a week
☐ Once a day	☐ Once a day

14) In which circumstances have you previously used deceptive (question a) and open-label (question b) placebo? (select all that apply)

a) **Deceptive** placebo

- ☐ Irrelevant - I never prescribe placebo
- ☐ Because there was no other available treatment
- ☐ In addition to a standard treatment
- ☐ Instead of a standard treatment in order to minimise side effects
- ☐ Because the patient demanded that specific treatment, which I considered being nothing but a placebo
- ☐ To calm an anxious patient
- ☐ To have something to give to the patient
- ☐ To avoid confrontation
- ☐ As a diagnostic tool (to distinguish between an organic and a functional / psychogenic disorder)
- ☐ For a functional / psychogenic disorder
- ☐ To treat non-specific symptoms
- ☐ Other

_____

b) **Open-label** placebo

- ☐ Irrelevant - I never prescribe placebo
- ☐ Because there was no other available treatment
- ☐ In addition to a standard treatment
- ☐ Instead of a standard treatment in order to minimise side effects
- ☐ Because the patient demanded that specific treatment, which I considered being nothing but a placebo
- ☐ To calm an anxious patient
- ☐ To have something to give to the patient
- ☐ To avoid confrontation
- ☐ As a diagnostic tool (to distinguish between an organic and a functional / psychogenic disorder)
- ☐ For a functional / psychogenic disorder
- ☐ To treat non-specific symptoms
- ☐ Other

_____

15) When you use a **deceptive** placebo, what do you say to the patient?

- ☐ Irrelevant - I never prescribe placebo
- ☐ Nothing
- ☐ It is a drug/medication
- ☐ It is a placebo
- ☐ Something along the lines of "We don´t quite know how this treatment works, but it sometimes does, so let's try it out"
- ☐ It is a treatment that might help but won´t cause any harm
- ☐ It is a treatment not generally used for their condition that might help
- ☐ It promotes self-healing
- ☐ Other

_____

16) Overall, it is ethically acceptable to use deceptive placebo treatments if there are no better treatment options in:

a) Purely organic disorders

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

b) Purely functional (psychogenic) disorders

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

c) Mixed organic and functional (psychogenic) disorders

strongly agree	mostly agree	mostly disagree	strongly disagree	I don´t know
☐	☐	☐	☐	☐

Please use the space below if you wish to make any further, general comments:

Please provide the following information about yourself:

Profession: ☐ Medical doctor

- ☐ Specialist: _____
  - ☐ Subspecialty: _____
  - ☐ Years of clinical practice since specialist accreditation: ___
- ☐ Doctor in training
  - ☐ Years of clinical practice since qualification: _____
- ☐ Medical student
- ☐ Other healthcare professional
  - ☐ Please specify: _____

Gender: ☐ male ☐ female ☐ Prefer not to say

Do you see many patients with functional (psychogenic) disorders?

☐ Yes ☐ No

☐ Tick this box if you are an expert in functional neurological disorder

☐ Tick this box if you are an opinion leader in FND

Your place of work:

☐ UK ☐ Europe other than UK

☐ North America ☐ Central & South America

☐ Asia ☐ Africa ☐ Oceania

Thank you very much for your participation.

For further information: Dr Anne-Catherine Huys (Association of British Neurologists fellowship project: The pathophysiology of functional movement disorders) Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, 33 Queen Square, floor 6, London, WC1N 3BG. Other investigators on this study: Prof Kailash Bhatia (Chief investigator, same department) and Prof Mark Edwards (St George's University and St George's Hospital).

A 10.3 Including healthy controls and medical patients

Q1: What are your initial thoughts? Do you think doctors should use deceptive placebo treatments if they think their patient could get a beneficial placebo effect from it?

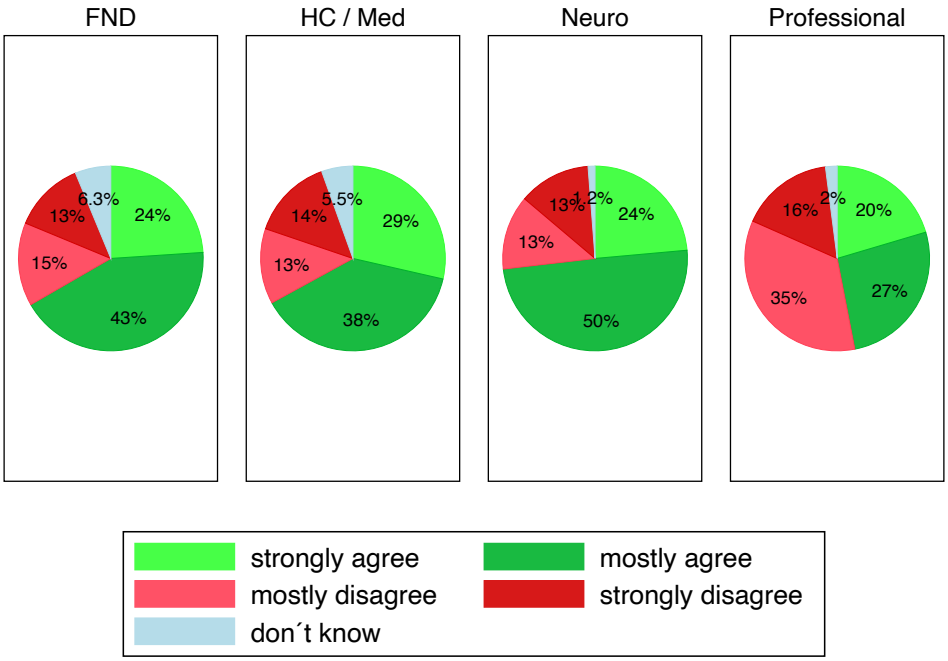


Figure 114: Q1

Q2: Do you think a placebo treatment could improve your symptoms?

(If you do not currently suffer from a medical condition, think about a medical problem you have experienced in the past)

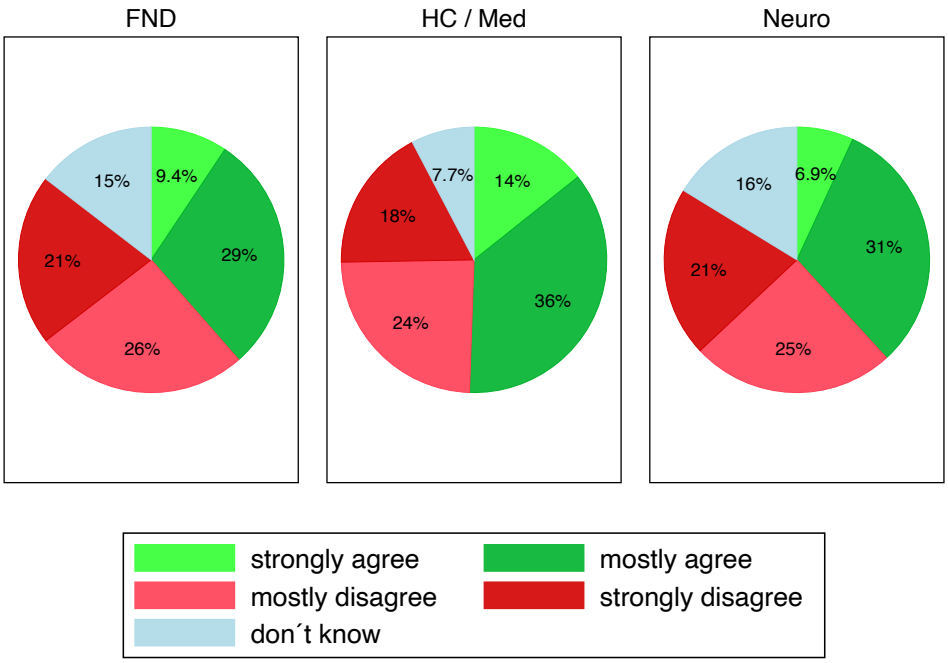


Figure 115: Q2

Q3: Considering potential risks of deceptive placebo treatment, where the patient does not know that the treatment is a placebo:

a) If doctors used deceptive placebo treatments, patients would lose trust in doctors and medicine.

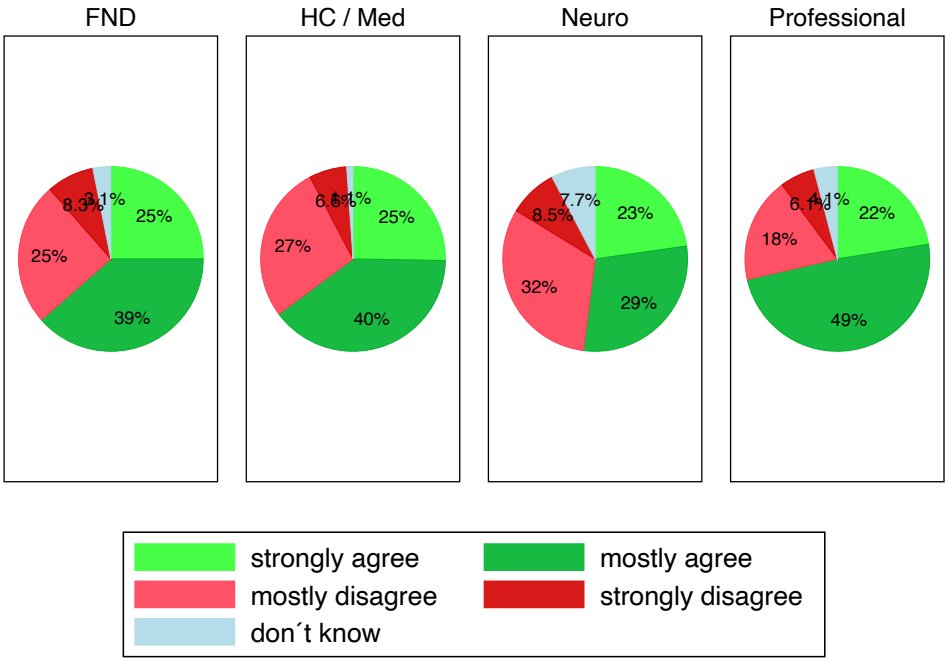


Figure 116: Q3a

b) By receiving deceptive placebo treatments, patients might become over reliant on medicines and interventions, rather than learn to cope and manage their symptoms themselves.

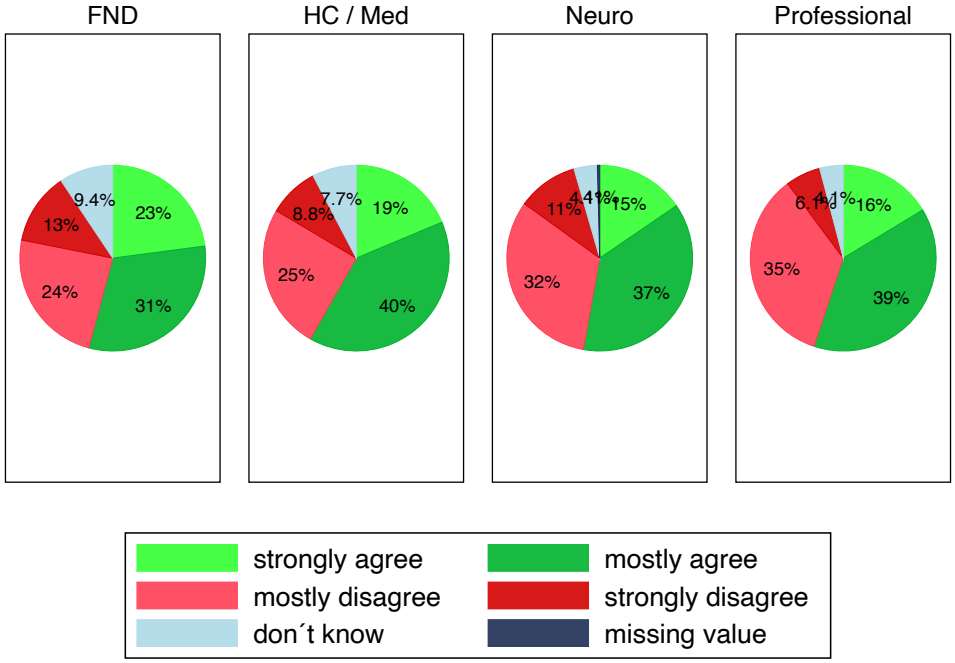


Figure 117: Q3b

Q4: Placebos work best when the patient does not know that the treatment they are receiving is a placebo (deceptive placebo). However, placebo can also work when the patient is told right from the start that the treatment is a placebo ("open-label placebo").

a) Placebo treatments should only be given in an open way. Patients should be told very clearly from the beginning if a treatment is a placebo, even if that meant it wouldn't work as well.

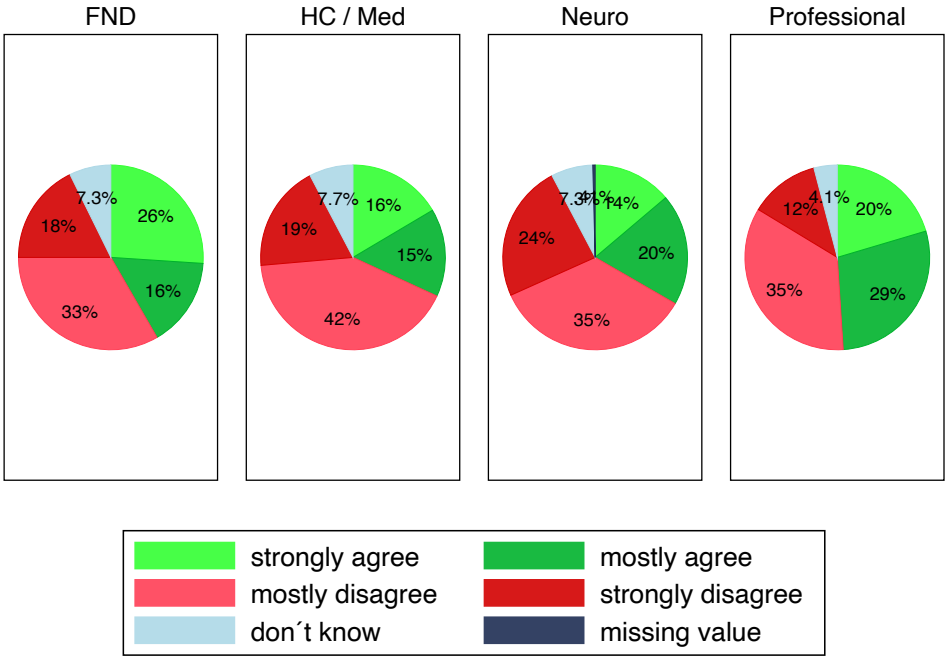


Figure 118: Q4a

b) If a doctor were to give a placebo, they should *not* tell the patient that it is a placebo so that it is as effective as possible, even if that meant the doctor not telling the full truth.

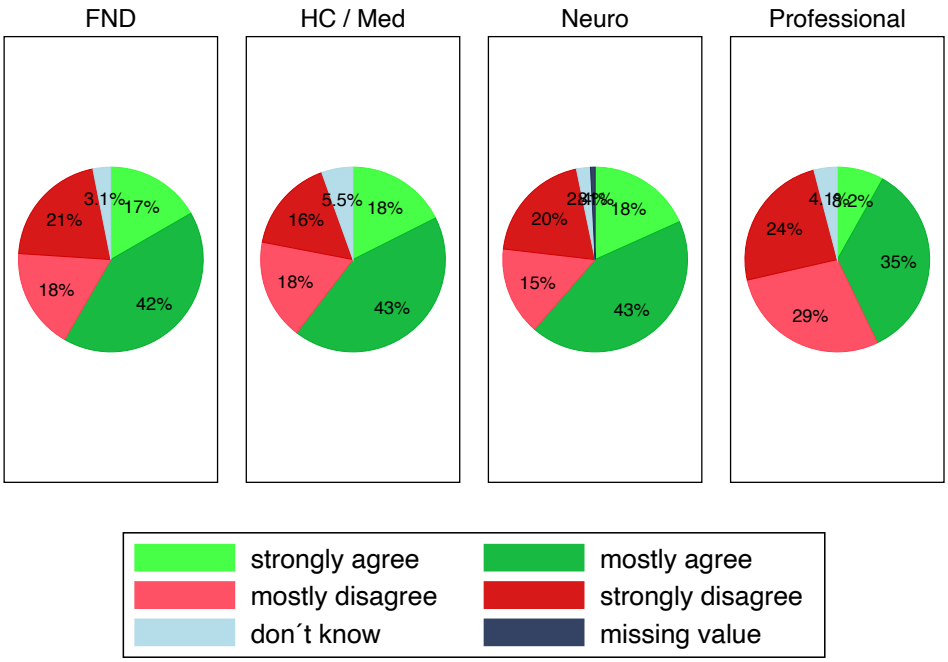


Figure 119: Q4b

c) It is acceptable for a doctor to give a placebo without telling the patient that it is a placebo and instead to remain vague and say: "This treatment sometimes works really well against the type of problems you have, so let's give it a try."

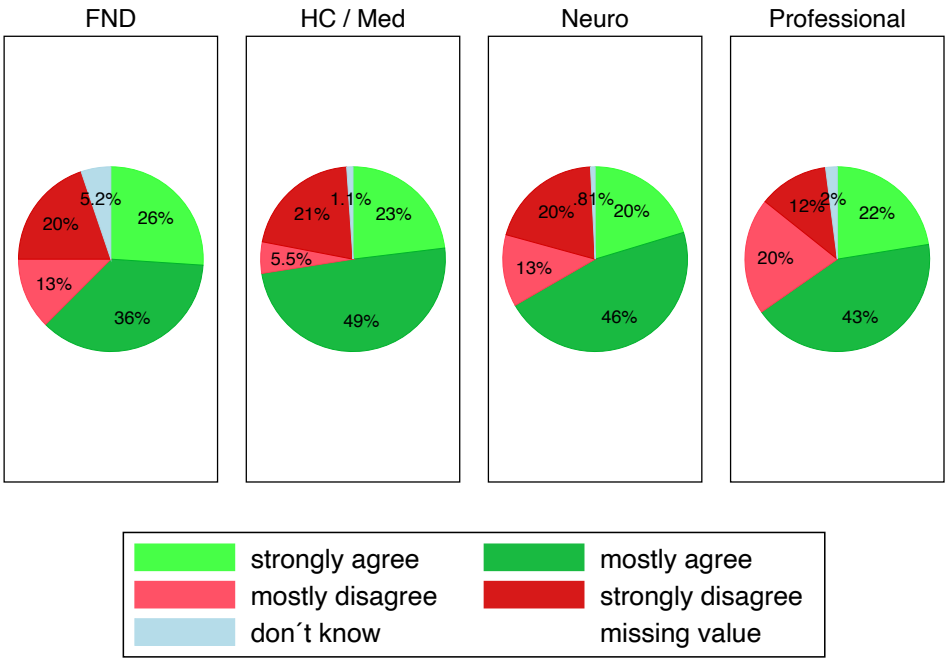


Figure 120: Q4c

d) I think that open-label placebo treatments (telling the patient that it is a placebo and that placebos are powerful) work just as well as deceptive placebo treatments (not telling the patient that it is a placebo).

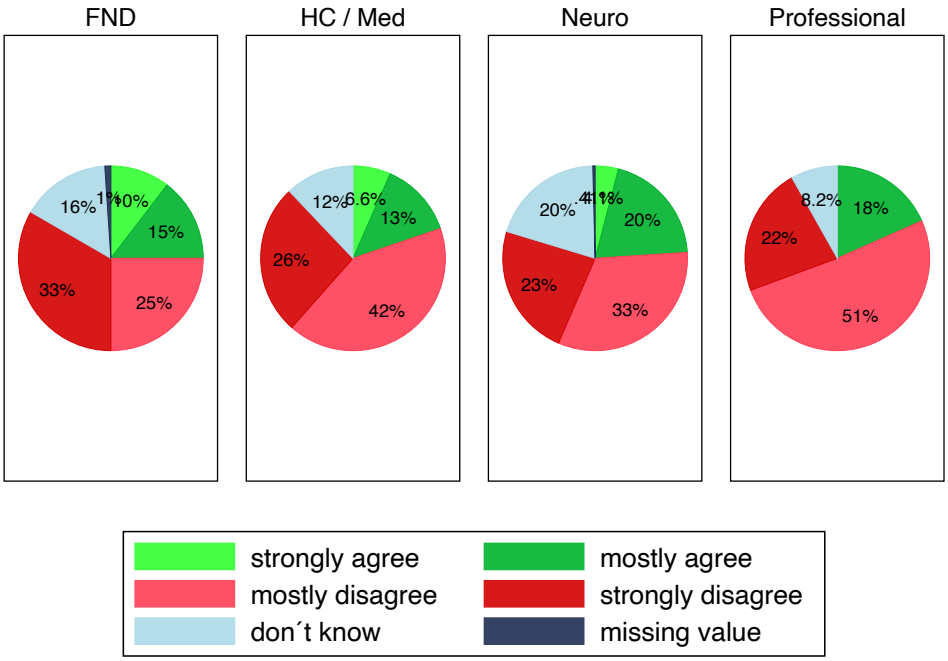


Figure 121: Q4d

e) **Imagine your doctor giving you a placebo treatment for a medical problem. When would you want your doctor to tell you that the treatment is a placebo? *Select all that apply***

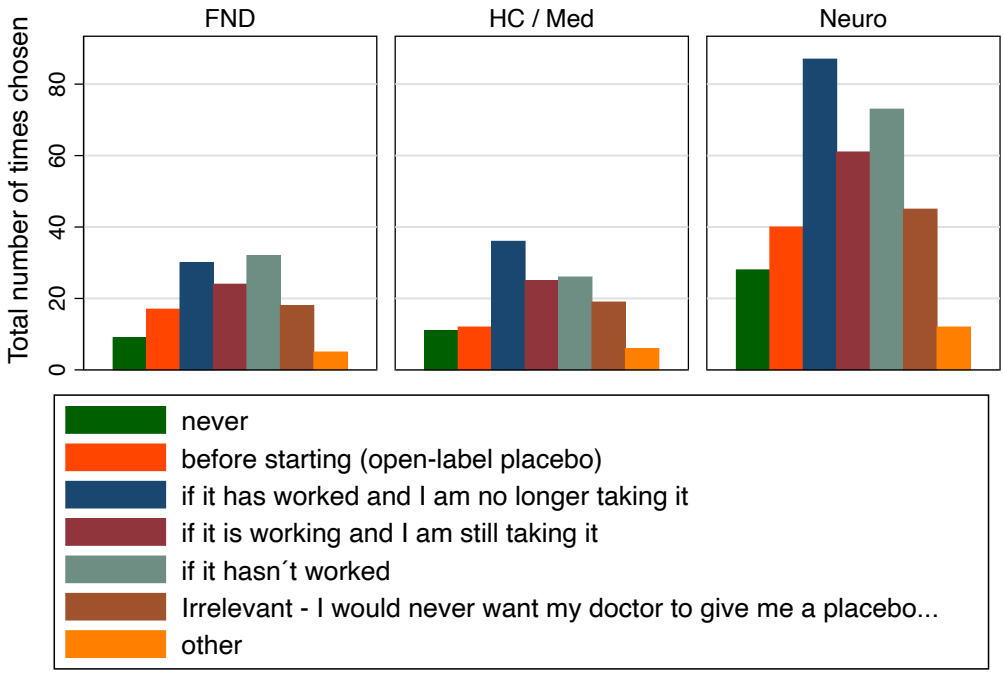


Figure 122: Q4e

Q5: Although nearly any condition can be associated with a placebo effect, only some conditions can show it to an extreme degree. A placebo could therefore be used to help make a diagnosis of these types of conditions. It is acceptable to use a deceptive placebo as a diagnostic tool in such cases.

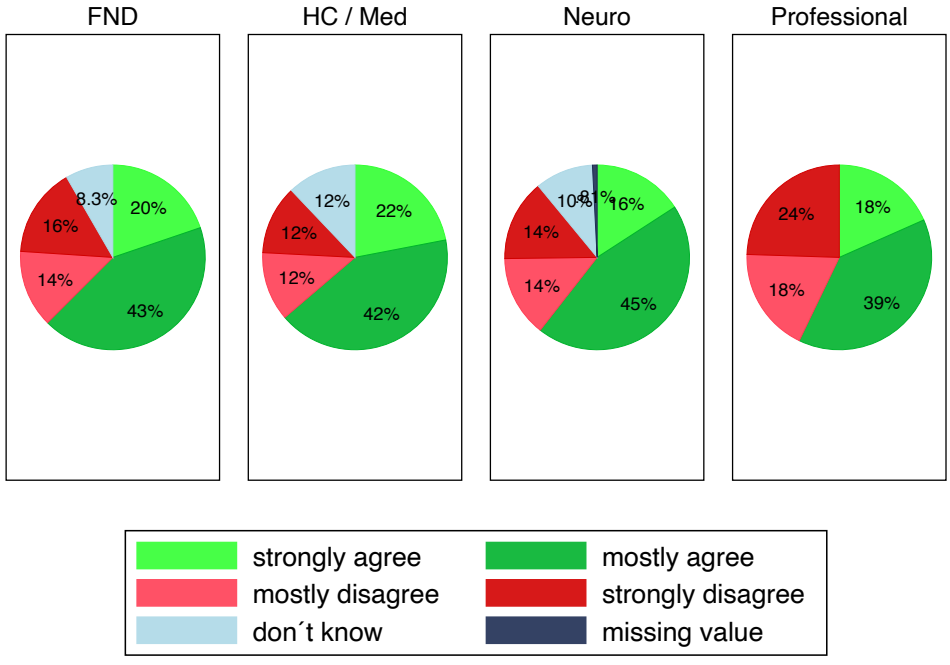


Figure 123: Q5

Q6: Some disabling conditions sometimes show strong placebo responses, with full recovery. In such cases, if standard treatments are unsuccessful, a doctor should attempt the following:

a) *deceptive* placebo

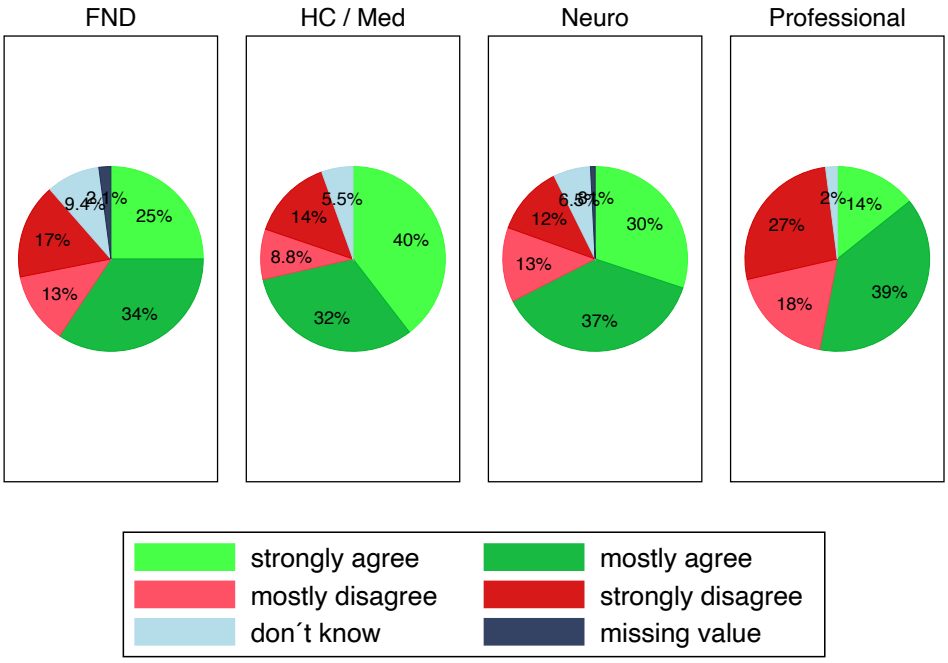


Figure 124: Q6a

b) *open-label* placebo

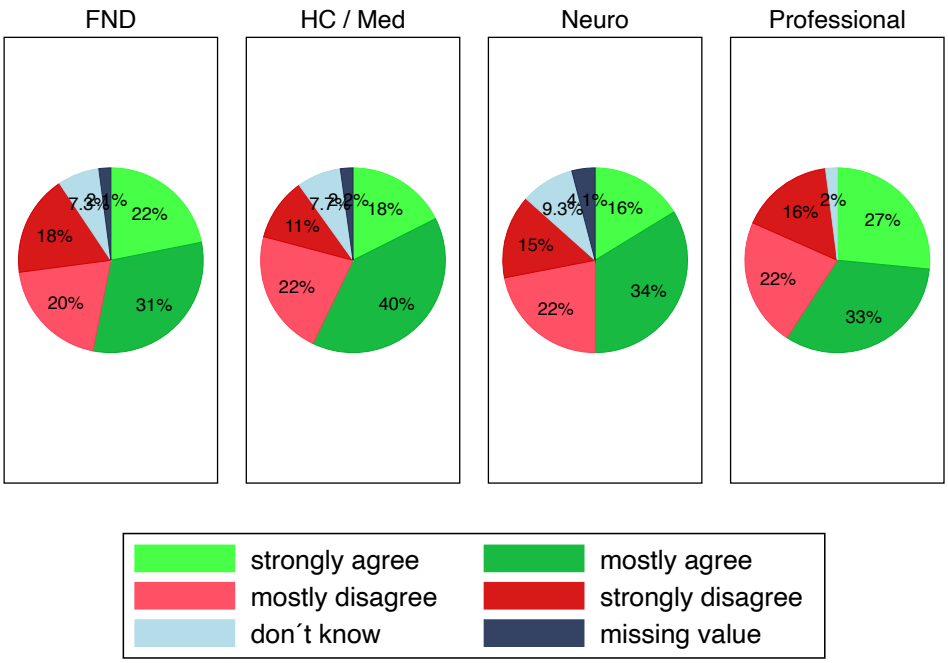


Figure 125: Q6b

Q7: An active (standard) drug will work better if it is given by a doctor the patient trusts fully, than if it is given by a doctor the patient trusts less.

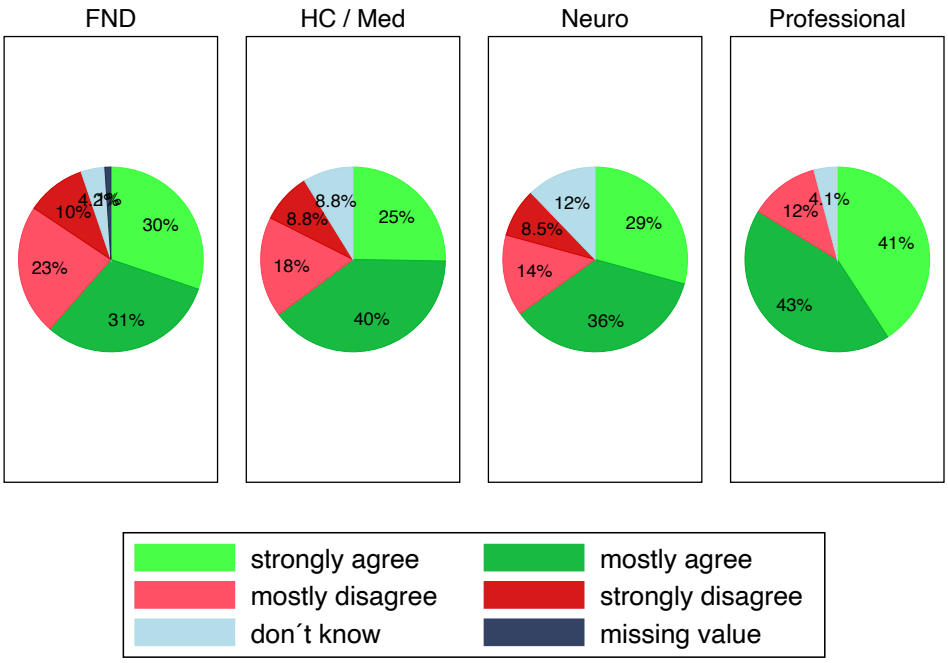


Figure 126: Q7

Q8: If a patient fully trusts a doctor, and that doctor tells the patient that their medical problem can improve or disappear if the patient believes it will, then this would work just as well as a placebo treatment.

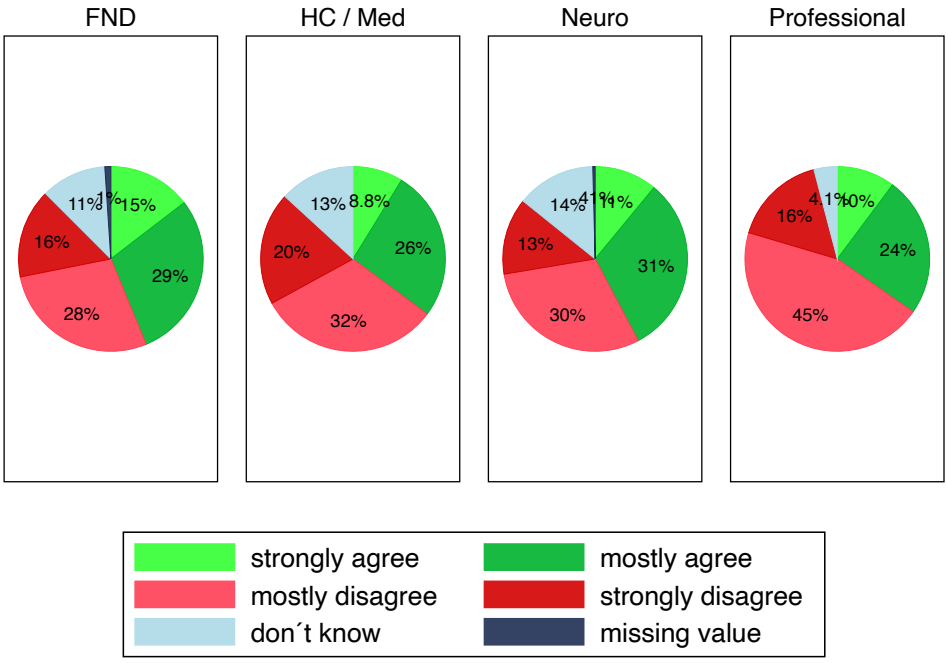


Figure 127: Q8

Q10: A 40-year-old man cannot move his legs and has been wheelchair-bound for 4 years despite many different treatments. All tests are normal and specific features on examination make the doctors diagnose a functional neurological disorder. This type of disorder is real and common. It may improve or persist. The doctor should give him the following:

a) a *deceptive* placebo

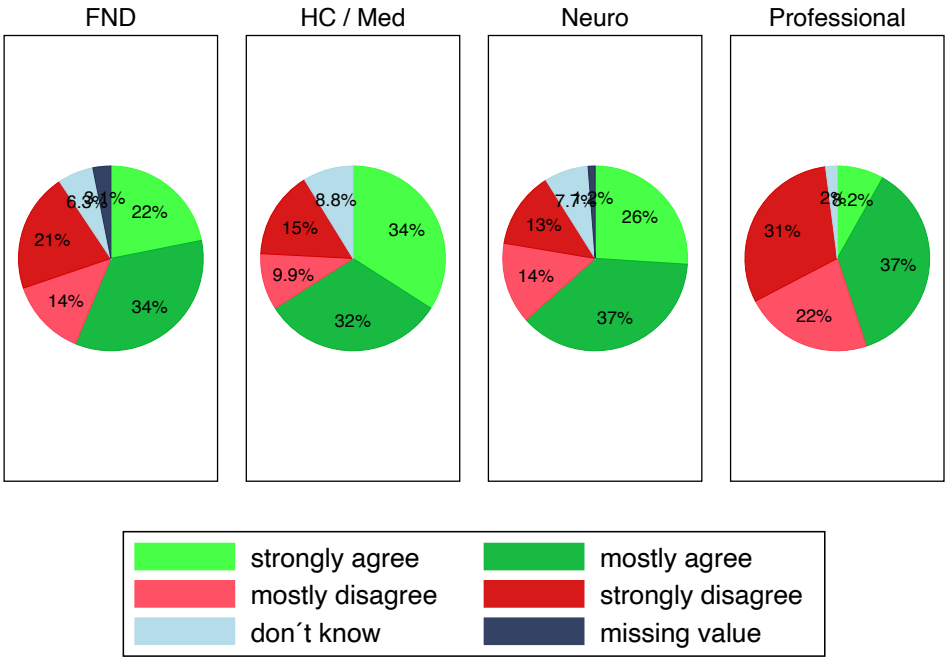


Figure 128: Q10a

b) an *open-label* placebo drug

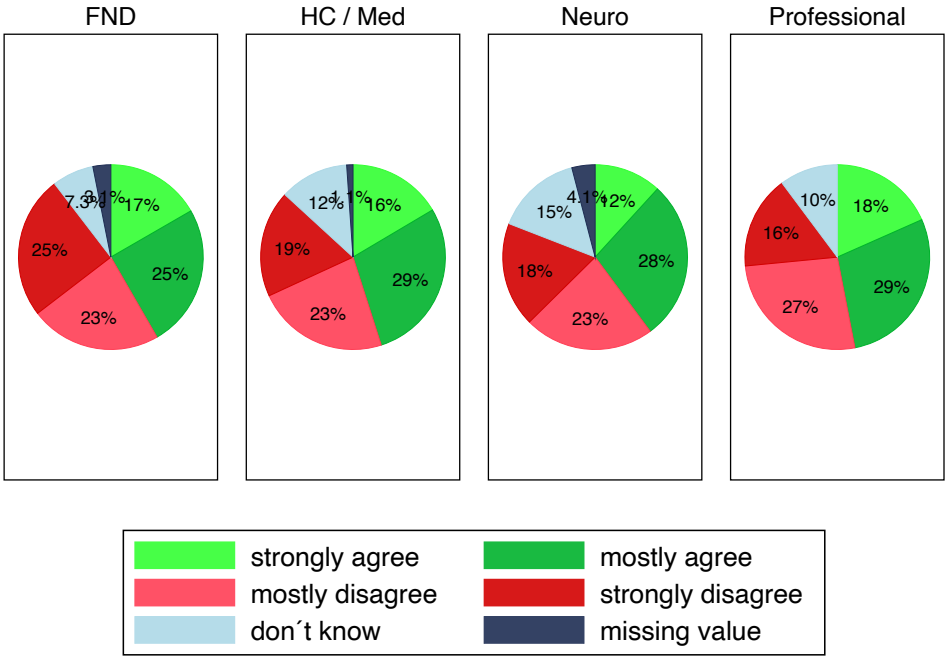


Figure 129: Q10b

Q11: Now that you have answered some more questions, we would like to ask you the same question as at the beginning. Do you think doctors should use deceptive placebo treatments if they think their patient could get a beneficial placebo effect from it? (Please don't go back and change your initial answer)

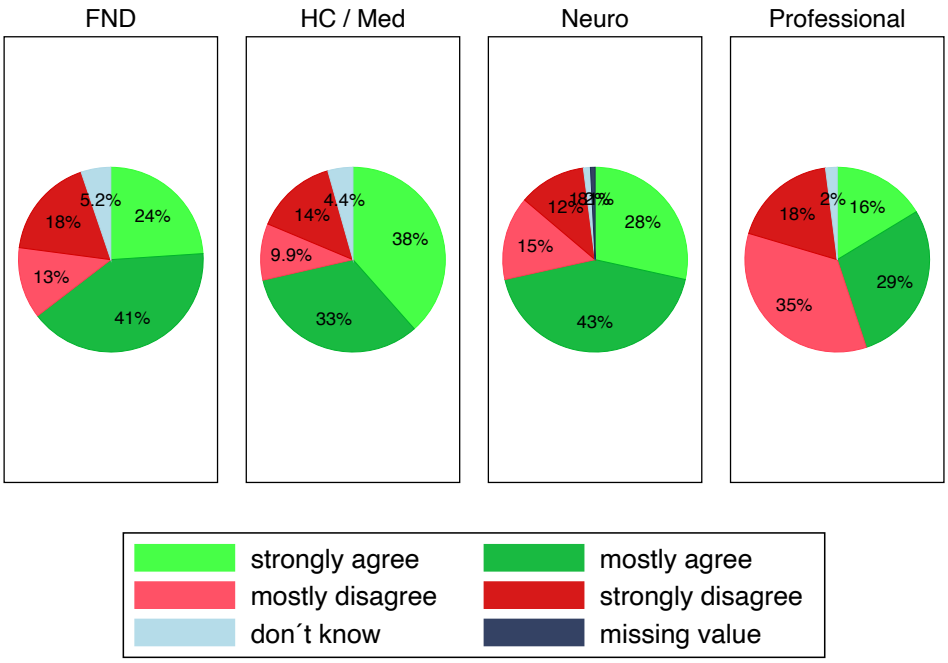


Figure 130: Q11