Original research

Distinguishing functional from primary tics: a study of expert video assessments

Antigoni Rigas,1 Tina Mainka 2,1,2 Tamara Pringsheim,3,4,5 Alexander Münchau,6 Irene Malaty,7 Yulia Worbe,8 Andrea E Cavanna,9,10,11,12 Andrew John Lees,13 Anthony E Lang 14, Davide Martino,3,4 Christos Ganos 1

ABSTRACT

Background Reliably applied criteria to differentiate functional from primary tics are lacking. In the absence of biological markers, the development of new diagnostic criteria to assist clinicians is predicated on expert judgement and consensus. This study examines the level of diagnostic agreement of experts in tic disorders using video footage and clinical descriptions.

Methods Using a two-part survey, eight experts in the diagnosis and management of tics were first asked to study 24 case videos of adults with primary tics, functional tics or both and to select a corresponding diagnosis. In the second part of the survey, additional clinical information was provided, and the diagnosis was then reconsidered. Inter-rater agreement was measured using Fleiss’ kappa. In both study parts, the factors which influenced diagnostic decision-making and overall diagnostic confidence were reviewed.

Results Based on phenomenology alone, the diagnostic agreement among the expert raters was only fair for the pooled diagnoses (κ=0.21) as well as specifically for functional (κ=0.26) and primary tics (κ=0.24). Additional clinical information increased overall diagnostic agreement to moderate (κ=0.51) for both functional (κ=0.6) and primary tics (κ=0.57). The main factors informing diagnosis were tic semiology, age at tic onset, presence of premonitory urges, tic suppressibility, the temporal latency between tic onset and peak severity, precipitants and tic triggers and changes in the overall phenotypic presentation.

Conclusions This study confirmed that in the absence of clinical information, the diagnostic distinction between primary and functional tics is often difficult, even for expert clinicians.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The distinction of primary from functional tics is often difficult. The relatively recent increase in prevalence and recognition of functional tics and the differences in treatment approaches between these aetiologies necessitate clinical diagnostic consensus. However, the validity of existing classifiers remains uncertain and there is little agreement as to the exact phenomenological boundaries between primary and functional tics.

WHAT THIS STUDY ADDS

⇒ This study demonstrates that it is not possible to distinguish primary from functional tics reliably based on phenomenology alone and that, even when key diagnostic points from the clinical history are provided, differences in expert opinion occur. Useful classifiers include age at tic onset, presence of premonitory urges, tic suppressibility, temporal evolution of symptoms, changes in phenotypic presentation and presence of contextual factors and triggers related to tics.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study highlights the imperative need to develop more accurate phenomenological definitions of tics, including novel diagnostic criteria for the different aetiologies and to identify reliable biomarkers that may allow disentangling between primary and functional tics. Until then, clinicians are advised to retain diagnostic humility when approaching challenging clinical areas such as this one.

INTRODUCTION

Tic disorders are among the most common hyperkinetic movement disorders in childhood and may also affect adults with a direct impact on their health and quality of life. The most prevalent tic aetiologies are primary tic disorders, such as Tourette syndrome (TS), but there is a wide range of differential diagnoses, including functional neurological disorder. Historically, the issue of functional tics has been at the centre of a prolonged and heated debate both in neurology and psychiatry with particular focus on the diagnostic classifiers of such cases and their clinical and pathophysiological distinction from primary tics.1 However, perhaps owing to the lack of more advanced neuroscientific and therapeutic tools at the time, this faded from focus for a longer period. In recent years, there has been a renewed interest in this discourse, specifically triggered by the growing incidence of cases with atypical characteristics from those observed in primary tic disorders.2-6 Moreover, during the COVID-19 pandemic, there has been an even greater increase of such cases,7-11 many of which have attracted the attention of millions in social media, further fueling the old discussion as to how to distinguish functional from primary tics.
To date, several phenomenological classifiers have been proposed to discern primary tic phenomena from functional tics. These diagnostic aids have been developed by observing the typical patterns of tics documented in people with primary tic disorders and contrasting these to movements and behaviours that grossly differ. However, in the absence of an established diagnostic standard or biomarker for either aetiology, the validity of such classifiers remains uncertain. Moreover, there is little consensus as to the exact phenomenological boundaries between primary and functional tics. Importantly, it remains unclear how to diagnostically approach cases where primary tics may coexist with functional tics, even though the combination is not uncommon. According to a recent international survey of members of the Movement Disorders Society, the second most common differential diagnosis to primary tics was functional tics, and the coexistence of the two diagnoses was reported to be as high as 25%.  

To accelerate progress towards the definition of phenomenological classifiers and aid the diagnostic distinction between primary and functional tics, experts with longstanding clinical and research experience in tic disorders and members of the Tic Disorders and Tourette Syndrome Study Group of the International Movement Disorder Society were invited to participate in this case-based study. Experts were given 24 tic disorder cases previously diagnosed as either primary tics, functional tics or both as part of a two-step survey. In the first part of the study, expert clinicians were only shown the videos of each case with key phenomenological features and were requested to provide a diagnosis based on phenomenology alone. In the second part, additional information from clinical history and examination was provided to assess whether this led to diagnostic reclassification. The goal of the study was to explore the level of diagnostic agreement of experts in tic disorders on the basis of phenomenology alone and to determine the key factors that increase diagnostic consensus and confidence in discerning primary and functional tics, or their coexistence.

METHODS
A case-based, two-part survey was created using the REDCap software and presented to eight movement disorder experts with longstanding clinical and research experience in tic disorders (AM, TP, IM, YW, AEC, AJL, DM, AEL). The first part was comprised of videos of 24 adults with tic disorders (14 men; mean age 26.7 ± 10.6 years) who were seen at the tic disorders and TS clinics of the senior author (CG). Cases were selected based on their phenomenology and clinical history, as well as the given diagnosis in clinic, which was either that of a primary tic disorder, a functional tic disorder or a primary tic disorder overlaid with functional tics. All videos were captured upon admission, video editing for 2.5 min, overlaying functional tics, and presented to eight movement disorder experts each case. Each of the experts was then requested to provide a diagnosis based on their phenomenology alone and/or other aetiologies (functional tics); the diagnosis of a primary tic disorder, most likely of functional and/or other aetiologies (functional tics); (4) non-tic disorder. The fourth diagnostic category was added to allow diagnosing phenomena that could, for some experts, semilogically strongly depart from the rubric of tics (as discussed in Kurvits et al.). The level of confidence for each provided diagnosis was captured on a scale from 0 to 100, as were the key phenomenological factors that led to each diagnosis. These included: the semiology of observed behaviours (ie, type of tics), their severity and body distribution as well as their variability. A fifth category of ‘other factors’ captured additional information that led to diagnosis.

In the second part of the survey, experts were given additional standardised historical information on each case. This information included age at onset of abnormal behaviours, clinical progression, the presence of sensory phenomena preceding the repetitive behaviours, their amenability to voluntary suppression, their impact on quality of life, the presence of additional medical diagnoses and the intake and effects of any medication. Based on this information, experts were then queried whether they would like to keep or reconsider their original diagnosis (from part 1), their current level of confidence (on a scale of 0–100, where 100 indicates absolute confidence) in the final diagnosis and the top factors that informed their decision. These now included age at presentation, age of onset of repetitive behaviours, presence of precipitants/contextual factors, type of first tic, changes in clinical presentation, time course from onset to maximum severity, presence of premonitory urges, ability to voluntarily suppress repetitive behaviours, presence of additional diagnoses as well as additional findings on clinical and additional investigations, other than those demonstrated in video. A further category captured ‘other factors’ (presented as free text) that informed final diagnosis. The full survey is found in the supplement (online supplemental file 1).

The level of diagnostic agreement between expert raters for parts 1 and 2 (ie, phenomenology alone; and phenomenology with additional clinical information) was computed using Fleiss’ kappa. Kappa values between 0 and 0.20 were determined as slight agreement, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial and 0.81–1 as almost perfect. The SPSS software V29 was used for all statistics. In two instances, specific data (tic phenomenology for case 5; top factors that lead to final diagnosis for case 13) could not be obtained due to a technical error in Redcap programming, and analyses were conducted without these specific datapoints. Kruskal-Wallis analysis was used to measure the effect of ‘diagnosis’ on the variance of the 0–100 scale-based judgement of diagnostic confidence and variability. Confidence between primary and final diagnosis was compared using the Wilcoxon test. Statistical significance was set at the p<0.05 threshold.

The data that support the findings of this study are available in the supplement. The complete data set of all responses is available on reasonable request to the corresponding author.

RESULTS
The clinical characteristics of the 24 video cases are presented in online supplemental table 2.

From 184 possible responses for each of the phenomena (data from 23/24 video cases), simple motor tics were detected 148 times by the eight raters, followed by complex motor tics in 109 instances. Simple phonic tics and complex phonic tics were observed 96 and 32 times, respectively. Tic-like behaviours uncommon for primary tics were noted 41 times. Copropheno-nema were detected 37 times, whereas echophenomena and...
paliphenomena 1 and 5 times only. Experts noted stereotypies eight times, and the phenomenological category of ‘other non-repetitive behaviours’ was selected 10 times. online supplemental table 3 provides a breakdown of detection frequency per case.

Based on the video-documented phenomenology of the 24 cases, the overall diagnostic agreement among the expert raters was fair (κ=0.21; 95%CI 0.152 to 0.26, p<0.001; see online supplemental table 4 for experts’ diagnoses per case). Examined per diagnosis, inter-rater agreement was fair for functional and primary tics (κ=0.26; 95%CI 0.181 to 0.332, p<0.001 and κ=0.24; 95%CI 0.166 to 0.317, p<0.001, respectively), but slight for primary tics coexisting with functional tics (κ=0.08; 95%CI 0.007 to 0.158, p=0.032), as also for the diagnosis of a non-tic disorder (κ=0.03, 95%CI –0.044 to 0.108, p=0.408). The median diagnostic confidence was 77.5 (IQR 64 to 90) and was highest for the diagnosis of primary tic/TS (median: 85; IQR 70 to 91), followed by functional tics (median: 76.5, IQR 66.5 to 87.5, H(3)=37.757, p<0.001) (see table 1).

The top factor driving the diagnostic distinction between primary and functional tics based on video evaluation alone was phenomenology (list of frequencies of reported factors provided in table 2).

Tic variability was significantly higher for cases diagnosed as functional tics (median: 75.5; IQR 59.5 to 85), and for those with overlap of primary and functional tics (median 66; IQR 50 to 71) compared with the diagnosis of primary tics (median: 20; IQR 10 to 30) and a non-tic disorder (median: 26; IQR 3.5 to 44.5, H(3)=83.804, p<0.001). Experts reported for 178 times (93% of all expressed judgements, that is, 24 cases rated by eight independent raters) that additional information was needed to increase diagnostic confidence. Most common queries included information about the age of tic onset, the presence of precipitants and contextual factors associated with tic onset and the temporal course of clinical symptom evolution.

When provided with additional information, the overall diagnostic agreement of experts increased to moderate (κ=0.51; 95%CI 0.456 to 0.565, p<0.001; see online supplemental table 4 for experts’ diagnoses per case). Inter-rater agreement was moderate for the diagnoses of functional (κ=0.6; 95%CI 0.528 to 0.679, p<0.001) and primary tics (κ=0.57; 95%CI 0.492 to 0.644, p<0.001) and fair for primary tics coexisting with functional tics (κ=0.33, 95%CI 0.254 to 0.405, p<0.001). The diagnosis of a non-tic disorder was applied at this stage in only one case and by one expert only (κ=−0.005; 95%CI −0.081 to 0.07, p=0.892) but was not further specified. Confidence in the final diagnosis was significantly higher than based on phenomenology alone (median: 92.5; IQR 80 to 100; Z=−9.223, p<0.001). Diagnostic confidence was highest for the diagnosis of a primary tic disorder (median: 100; IQR 89.5 to 100), followed by the diagnosis of functional tics (median: 92.5; IQR 80 to 99, H(3)=43.374, p<0.001) (also see table 1). The top clinical information factors most relevant for the diagnosis of primary tics were knowledge on the presence of premonitory urges and tic suppressibility as well as the age at onset of tics. The top factors that allowed the raters to reach a final diagnosis of functional tics were the type of precipitants that were reported to be associated with the manifestation of tics, the time course from onset to maximum tic severity and the age at onset of tics. The most common factor informing the diagnosis of coexisting primary and functional tics was an overall change in phenotypic presentation. Table 3 provides a list of frequencies of top-rated factors for each diagnosis.

**DISCUSSION**

This study assessed the level of agreement between tic experts in diagnosing 24 cases with tics as either primary, functional or both. A two-step approach was used, in which each expert was expected to make a diagnosis based on patient videos alone, and then again after receiving details of the clinical history. The findings emphasise that it is difficult to distinguish primary tics from functional tics based on observation of the movement disorder alone and that clues from the clinical history are needed. These include the age at tic onset, the temporal evolution of symptoms, changes in overall phenotypic presentation and the presence of contextual factors and triggers related to tic behaviours.

The main goal of this study was to explore whether experts would agree on the diagnostic distinction between primary and functional tics, or their coexistence, on the basis of clinical observation (video-presented cases) alone. This topic has been at the centre of a long-standing debate in tic disorders, specifically in relation to whether phenomenological classifiers are sufficient to inform diagnostic consensus and has been fuelled recently by a marked increase in the number of people diagnosed with functional movement disorders that seem to have been associated with exposure to social media platforms. Some experts have argued that distinguishing between primary and functional tics is straightforward and can be achieved by simply observing

---

**Table 1** Diagnostic confidence for all 24 cases together (all diagnoses) and split for each diagnosis at parts 1 (video-based diagnosis) and 2 (with additional information provided).

<table>
<thead>
<tr>
<th>Diagnostic confidence</th>
<th>All diagnoses</th>
<th>Primary tics/Tourette syndrome</th>
<th>Primary and functional tics</th>
<th>Functional tics</th>
<th>Non-tic disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 1</td>
<td>77.5 (64–90)</td>
<td>85 (70–91)</td>
<td>60 (50–72)</td>
<td>76.5 (66.5–87.25)</td>
<td>61 (49.5–63)</td>
</tr>
<tr>
<td>Part 2</td>
<td>92.5 (80–100)</td>
<td>100 (89.5–100)</td>
<td>80 (70–90)</td>
<td>92.5 (80-99)</td>
<td>90*</td>
</tr>
</tbody>
</table>

*Diagnosis given only once by only one expert.

---

**Table 2** Top factors leading to the diagnosis (part 1, video-based only)

<table>
<thead>
<tr>
<th></th>
<th>Primary tics/Tourette Syndrome</th>
<th>Primary and functional tics</th>
<th>Functional tics</th>
<th>Non-tic disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Semiology</strong></td>
<td>98.1% (104/106)</td>
<td>92.6% (25/27)</td>
<td>98.1% (53/54)</td>
<td>100% (5/5)</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td>11.3% (12/106)</td>
<td>14.8% (4/27)</td>
<td>13% (7/54)</td>
<td>100% (5/5)</td>
</tr>
<tr>
<td><strong>Body Distribution</strong></td>
<td>63.2% (67/106)</td>
<td>51.9% (14/27)</td>
<td>55.6% (30/54)</td>
<td>60% (3/5)</td>
</tr>
<tr>
<td><strong>Variability</strong></td>
<td>30.2% (32/106)</td>
<td>70.4% (19/27)</td>
<td>64.8% (35/54)</td>
<td>20% (1/5)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>18.9% (20/106)</td>
<td>37% (10/27)</td>
<td>16.7% (9/54)</td>
<td>100% (5/5)</td>
</tr>
</tbody>
</table>

the abnormal movement over a period of time, while others have questioned this belief. The low level of diagnostic agreement based on case videos in this study provides support for the latter view. However, even though diagnostic agreement was low, the experts did feel that tic severity was the most important factor informing their overall decision-making and highlighted the importance of the cranio-caudal distribution of primary tics, and tic variability for functional tics. The experts were in agreement that additional information was required, specifically related to the onset, the presence of associated contextual factors or precipitants, and the temporal course of symptoms.

When clinical information was added, overall diagnostic agreement improved from fair ($k=0.21$) to moderate ($k=0.51$), which was also paralleled by an increase in diagnostic confidence. Although the age of tic onset was judged in all categories as a helpful distinguishing criterion, the presence of premontory urges and the amenability of tics to voluntary tic inhibition were felt to be the most helpful factors to diagnose primary tics, even though they are not part of the current definition used to describe tics. In contrast, the diagnosis of functional tics was informed by the presence of specific precipitants and contextual factors associated with tic manifestation (e.g., following COVId-19 vaccination or an episode of “collapse” at work), as well as the time course between tic onset and maximum severity. Physical and psychological precipitants associated with the acute onset of functional tics have been reported in the recent marked increase in functional tics observed during the past 3 years, as also documented in other functional movement disorders.

In primary tics, stressors may lead to exacerbations of tic severity but have not been linked to tic onset. The time course of tic manifestation was a further useful classifier, as many cases of functional tics develop acutely or subacutely and may reach a "full blown" clinical picture within a matter of hours, days, or weeks.

Despite the improvement in diagnostic reliability with access to the clinical data, it is noteworthy that the maximum overall level of agreement was still only moderate. Although there was agreement for several cases, diagnostic difficulties for overlapping phenomena, mostly for the diagnosis of a primary tic disorder overlaid with functional tics occurred. Indeed, diagnostic agreement here only improved from slight ($k=0.08$) to fair ($k=0.33$). In the absence of clear categorical criteria to distinguish primary and functional tics, which may also present with similar semiology, this diagnosis remains challenging, even though many movement disorder clinicians with experience in diagnosis and managing patients with tics believe that this combination is quite common. Of note, changes in phenotypic presentation were deemed as the most useful factor in the clinical history to inform this diagnostic possibility. A related challenging diagnostic judgement relates to whether all the observed behaviours fall under the tic rubric. Our experts identified 'tic-like behaviours uncommon for primary tics' 41 times, and two experts selected the diagnosis of a non-tic disorder based on video-evaluation alone five times in total. Importantly, the diagnosis of a non-tic disorder was retained by one expert even after the additional clinical information provided. Overall, our results highlight the existing difficulties, even for experts, to reliably apply the operational definition of tics, as it appears that the term tic is used to indicate a diversity of repetitive behaviours (also see).

Diagnostic disagreement between expert clinicians may have been the result of differing criteria used to establish a functional tic diagnosis, and differences in practical experience with functional tic patients based on referral biases and practice volumes. At the time of performing this analysis, diagnostic clues for the diagnosis of functional tic disorder had been discussed in several publications but specific criteria were not formally established, leaving the clinicians involved in this project to mainly rely on their own clinical intuition to make this diagnosis. Furthermore, clinical volumes with patients with functional tics varied between expert clinicians, which likely influenced individual expertise and confidence in making a functional tic diagnosis.

Our study could not assess the accuracy of our experts' final diagnostic judgement, due to the lack of diagnostic standards or biomarkers. Very recently, after our data collection was complete, a single-centre study developed a set of diagnostic criteria that yielded encouraging discriminatory capacity to differentiate between the diagnoses of 'functional tic disorder' and 'primary tic disorder'. Although differentiation by these criteria required the presence of at least 2 of 7 different phenomologal characteristics potentially detectable through direct observation alone, it also required additional clinical information that included type of onset, comorbidity, and even sex at birth and family history. Even more recently, consensus-based diagnostic criteria for the clinical diagnosis of functional tic like behaviours have been published by an international group with expertise in tic disorders. A 'clinically definite' diagnosis requires the presence of three major criterion which allow clinicians to differentiate functional tic like behaviours from tics—age of symptom onset (age 12 and older), rapid onset and evolution of symptoms (over hours to days) and the presence of four of

### Table 3: Top factors leading to the diagnosis (part 2, additional clinical history)

<table>
<thead>
<tr>
<th>Age at presentation</th>
<th>Primary tics/Tourette syndrome</th>
<th>Primary and functional tics</th>
<th>Functional tics</th>
<th>Non-tic disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>32.2% (29/90)</td>
<td>39.5% (15/38)</td>
<td>41.8% (23/55)</td>
<td>100% (1/1)</td>
<td></td>
</tr>
<tr>
<td>61.1% (55/90)</td>
<td>63.2% (24/38)</td>
<td>61.8% (34/55)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>11.1% (10/90)</td>
<td>50% (19/38)</td>
<td>63.6% (35/55)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>36.7% (33/90)</td>
<td>26.3% (10/38)</td>
<td>16.4% (9/55)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>12.2% (11/90)</td>
<td>71.1% (27/38)</td>
<td>21.8% (12/55)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>32.2% (29/90)</td>
<td>34.2% (13/38)</td>
<td>61.8% (34/55)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>73.3% (66/90)</td>
<td>36.8% (14/38)</td>
<td>3.6% (2/55)</td>
<td>100% (1/1)</td>
<td></td>
</tr>
<tr>
<td>57.8% (52/90)</td>
<td>23.7% (9/38)</td>
<td>10.9% (6/55)</td>
<td>100% (1/1)</td>
<td></td>
</tr>
<tr>
<td>32.2% (29/90)</td>
<td>36.8% (14/38)</td>
<td>20% (11/55)</td>
<td>100% (1/1)</td>
<td></td>
</tr>
<tr>
<td>1.1% (1/90)</td>
<td>2.6% (1/38)</td>
<td>1.8% (1/55)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>8.9% (8/90)</td>
<td>7.9% (3/38)</td>
<td>7.3% (4/55)</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

Data related to the selection of top factors is missing for one case, due to a technical error.

*Diagnosis given once by a single expert.
nine phenomenological features. While broad clinical applicability and usefulness of these criteria will need to be verified by other authors, their formulation aligns with our findings that phenomenology alone is insufficient to differentiate between functional and primary tic disorders.

The 24 cases that we selected to measure agreement among experts were designed to test clinicians’ ability to distinguish primary tic disorder, functional tic disorder or an overlap between the two. The ‘real-world’ diagnoses that these patients had received were not factored in the analyses, because it may have confounded the interpretation. A potential limitation of our study is the duration of the edited videos. Although we presented 2.5 min videos for each case, it could be argued that a longer observation would have allowed for greater agreement, for example, through a more detailed representation of how certain behaviours cluster in time. However, the edits were selected to depict all relevant clinical signs that each patient exhibited during their clinical presentation, and, therefore, accurately reflect the phenotype observed in clinic. Finally, although we selected several top factors as distilled from the existing literature for experts to choose from for each of the two study parts (phenomenology vs clinical information), it is possible that other informative factors were omitted. However, no other top factor was consistently brought up in the ‘others’ category of both top factors lists.

This study indicates that it is not possible to distinguish primary tics from functional tics with any level of confidence from short video clips alone and that even when key diagnostic points from the clinical history are also provided differences in expert opinion occur. This highlights the imperative need to develop more accurate phenomenological definitions of tics, including novel diagnostic criteria for the different etiologies as well as to identify reliable biomarkers that may allow disentangling between primary and functional tics. In the current study, the contrast between the fair to moderate achieved agreement at both steps and the individual high to very high confidence in diagnosis suggests that clinicians should retain diagnostic humility when approaching challenging clinical areas such as this one.

**Contributors**

AR: Research project: conception, organisation, execution; Statistical analysis: design, execution, Manuscript preparation: review and critique. TM: Research project: conception, organisation, execution; Statistical analysis: design, execution, Manuscript preparation: review and critique. TF: Research project: execution; Statistical analysis: review and critique; Manuscript preparation: writing of the first draft, review and critique. AM, IM, YW, AJL, AEL, DM: Research project: execution; Statistical analysis: review and critique; Manuscript preparation: review and critique. CG: Research project: conception, organisation, execution; Statistical analysis: design, execution; Manuscript preparation: writing of the first draft.

**Funding**

This research was supported by a VolkswagenStiftung (Freigeist) grant (AZ. 94 268) held by Christos Ganos.

**Competing interests**

None declared.

**Patient consent for publication**

Not applicable.

**Ethics approval**

This study involves human participants and was approved by Charité University Medicine Berlin local ethics committee (EA2/152/22). Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Data availability statement**

Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. Data beyond the ones included in the article or uploaded as supplementary information will be available upon reasonable request.

**Supplemental material**

This content has been supplied by the author(s). It has not been vetted by BMBI Publishing Group Limited (BML) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BML. BML disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BML does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access**

This is an open access article distributed in accordance with the Creative Commons Attribution Non-Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**ORCID iDs**

Tina Mainka http://orcid.org/0000-0002-0597-2648
Yulia Worbe http://orcid.org/0000-0001-5903-9370
Anthony E Lang http://orcid.org/0000-0003-1229-3667
Davide Martino http://orcid.org/0000-0002-2217-0487
Christos Ganos http://orcid.org/0000-0001-8077-8530

**REFERENCES**


