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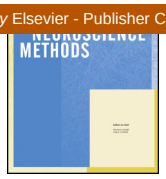

Quantitative evaluation of orofacial motor function in mice: The pasta gnawing test, a voluntary and stress-free behavior test

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HIGHLIGHTS

- The pasta gnawing test measures orofacial motor deficits.
- The pasta gnawing test is useful as an alternative to limb motor tests.
- The pasta gnawing test is useful to test progression of early onset disease models.
- The pasta gnawing test is stress-free and depends on voluntary behavior.

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ABSTRACT

Background: Evaluation of motor deficits in rodents is mostly restricted to limb motor tests that are often high stressors for the animals.
New method: To test rodents for orofacial motor impairments in a stress-free environment, we established the pasta gnawing test by measuring the biting noise of mice that eat a piece of spaghetti. Two parameters were evaluated, the biting speed and the biting peaks per biting episode. To evaluate the power of this test compared to commonly used limb motor and muscle strength tests, three mouse models of Parkinson's disease, amyotrophic lateral sclerosis and Niemann-Pick disease were tested in the pasta gnawing test, RotaRod and wire suspension test.
Results: Our results show that the pasta gnawing test reliably displays orofacial motor deficits.
Comparison with existing methods: The test is especially useful as additional motor test in early onset disease models, since it shows first deficits later than the RotaRod or wire suspension test. The test depends on a voluntary eating behavior of the animal with only a short-time food deprivation and should thus be stress-free.
Conclusions: The pasta gnawing test represents a valuable tool to analyze orofacial motor deficits in different early onset disease models.

1. Introduction

Measuring motor behavior in rodent disease models is often performed in long lasting tests with time consuming 'paper pencil' evaluations and under high stress conditions, e.g. in the RotaRod or challenging beam walk test. Especially testing of rodent models with a severe phenotype or increased probability of epileptic seizures sometimes leads to insufficient results due to incapability of the animals to perform the task. In 2011, Kane and colleagues noticed that while performing a pasta handling test (Vermicelli and Capellini handling test) for evaluation of the lesion rate of unilaterally 6-OHDA injected rats, not only the number of adjustments with each paw was altered, but also the biting noise changed (Kane et al., 2011).

We therefore developed the voluntary pasta gnawing motor test for mice with a minimum of experimenter's or equipment interference and thus a minimum of stress for the animals. Since eating displays a basal natural behavior and biting noise can also be easily recorded from a distance, we established quantitative analyses of this behavior. Additionally, we analyzed if the orofacial motor test represents a good alternative to the most commonly performed evaluations of limb associated motor tests.

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To analyze the suitability and value of the pasta gnawing test, we thus measured the biting behavior compared to well-established limb motor tests in three mouse models representing three different indications and already known to present limb motor deficits: I: Line 61 mice overexpress α-synuclein and are a model of Parkinson's disease [PD (Rockenstein et al., 2002)], a disease that is, next to shaking and gait disturbances, also characterized by difficulties in mastication and orofacial function which can be observed in moderate to advanced disease stages (Bakke et al., 2011). Swallowing disturbances can already manifest in early and mid-stage PD (Jones and Ciucci, 2016). II: homozygous TAR6/6 mice overexpress TARDBP (TDP-43) and are a model of amyotrophic lateral sclerosis [ALS (Wils et al., 2010)]. About 70% of ALS patients with spinal disease onset suffer from dysarthria and dysphagia (da Costa Franceschini and Mourao, 2015), though patients with bulbar ALS are generally more severely affected compared to patients with corticobulbar or spinal ALS (Langmore and Lehman, 1994). These disturbances depend on muscle weakness in orofacial muscles, specifically the tongue (DePaul et al., 1988; DePaul and Brooks, 1993). Dysphagia is already measurable at the initial diagnosis of the disease (Murono et al., 2015) and thus a very early symptom. III: NPC1$^{-/-}$ knockout mice are a model of Niemann-Pick disease type C1 [NPC1 (Loftus et al., 1997)] that belongs to the lysosomal storage diseases exhibiting neurological symptoms like unsteady gait, tremor and progressive dementia, but also dysphagia and dysarthria (Vanier, 2010). About 80% of NPC1 patients suffer from dysphagia (Garver et al., 2007), while in the adult form of the disease only 37% present dysphagia and 63% dysarthria (Sevin et al., 2007).

2. Materials and methods

All animals were bred and housed under identical conditions in individually ventilated cages on standardized rodent bedding (Rettenmayer®) in the AAALAC accredited animal facility of QPS-Austria. Cotton nestlets (Plexx®) were provided as nesting material. The room temperature was kept at approximately 24 °C and the relative humidity between 40 and 70%. Mice were housed under constant light-cycle (12 h light/dark). Dried pelleted standard rodent chow (Altromin®) and normal tap water were available to the animals *ad libitum*. Each individual animal was checked regularly for any clinical signs. Only male animals were used. Mice were housed in same sex groups of up to four animals. During weaning, less than 1 mm of the tail tip was cut from each animal and used for genotyping. Behavioral tests were always performed in the morning during the light cycle. Before the start of each behavioral test, animals were habituated to the experimental room for at least 1 h. Age groups were chosen according to the observed phenotype onset (first age group) and late stage phenotype (last age group) of each mouse model and thus represent relevant time points for possible compound tests. Behavioral tests were performed in the order as mentioned below. Animal studies complied with the ARRIVE guideline (Kilkenny et al., 2010) and the Austrian guidelines for the care and use of laboratory animals and were approved by the Styrian government, Austria.

2.1. Line 61 mice

Line 61 mice express human wildtype α-synuclein under control of the murine neuronal Thy-1 promoter. Compared to endogenous α-synuclein, the transgene is about 10-fold higher expressed (Rockenstein et al., 2002). Animals are a commonly used model of Parkinson's disease. Heterozygous mice were bred by pairing one heterozygous male with two non-transgenic (ntg) females or by pairing one ntg male with two heterozygous females and the heterozygous offspring was tested compared to ntg littermates. Only male animals at the age of 8, 12 or 24 weeks were tested cross-sectional.

2.2. TAR6/6 mice

TAR6/6 mice express the human wildtype TARDBP (TDP-43) under control of the murine neuronal Thy-1 promoter. In homozygous TAR6/6 mice the TARDBP protein concentration is about 3.8-fold higher compared to endogenous TARDBP (Wils et al., 2010). Animals are a commonly used model of amyotrophic lateral sclerosis. Homozygous mice were bred by pairing one heterozygous male with one heterozygous female and homozygous offspring was tested compared to ntg littermates. Only male animals at the age of 6 and 20 weeks were tested cross-sectional.

2.3. NPC1$^{-/-}$ mice

NPC1$^{-/-}$ mice have a spontaneous mutation in the Niemann-Pick type C1 gene (NPC1^{m1N}). Animals homozygous for the mutation show decreased sphingomyelinase and glucocerebrosidase activity and are thus a commonly used model of Niemann-Pick disease (Loftus et al., 1997). Homozygous mice were bred by pairing one heterozygous male with one heterozygous female and offspring was tested compared to ntg littermates. Only male animals were longitudinally tested at the age of 6 and 8 weeks.

2.4. Pasta gnawing test

The test was adapted from (Kane et al., 2011). Two hours prior to testing the food of all animals was removed and animals were single housed. One little piece of dry spaghetti (Goldmarke, Spaghetti No. 5) was given to each animal to become familiar with the novel food in the moment the regular food was removed. To measure biting noise the home cage was placed in a sound proof cabinet and each animal was recorded at a time by placing a microphone above the cage. Dry spaghetti pieces (approx. 1 cm long) were given into the cage (Fig. 1A). Afterwards, the biting noise was recorded for one minute and an interval of ten seconds was evaluated. During the pasta gnawing measurement, all animals were observed by an experimenter, to guarantee that the sound recording was taken while the animal was indeed eating the pasta. Acquisition was performed by using Behringer ECM 8000 microphone connected to a Steinberg Cl1 audio interface. Steinberg Wave Lab LE 7 was used as recording software. The acquired biting pattern was analyzed using Avisoft SASLab Pro 5.1 sound analyzing software (Fig. 1B, C). When analyzing the sound recordings, the experimenter additionally checked the sound quality acoustically by listening to the sound sequence with a headset to clearly identify biting events. Afterwards an intensity threshold line (see Fig. 1) was set to separate biting events from background noise. Two parameters were evaluated: I: biting speed (biting frequency; bites per second within a biting episode) and II: biting peaks per biting episode (number of bites during a biting episode). An exemplary video showing a pasta eating mouse is provided in Supplementary file 1. The acoustic file related to this video recorded with the Behringer ECM 8000 microphone is provided in Supplementary file 2. The corresponding waveform and spectrogram of the start of the video analyzed by Avisoft software is thus shown in Supplementary file 3.

2.5. Wire suspension test

The test evaluates the muscle strength of mice. A standard wire cage lid was used. The mouse was placed on the top of the lid. Afterwards, the lid was slightly shaken to cause the mouse to grip the wires, and then turned upside down. Duct tape placed around

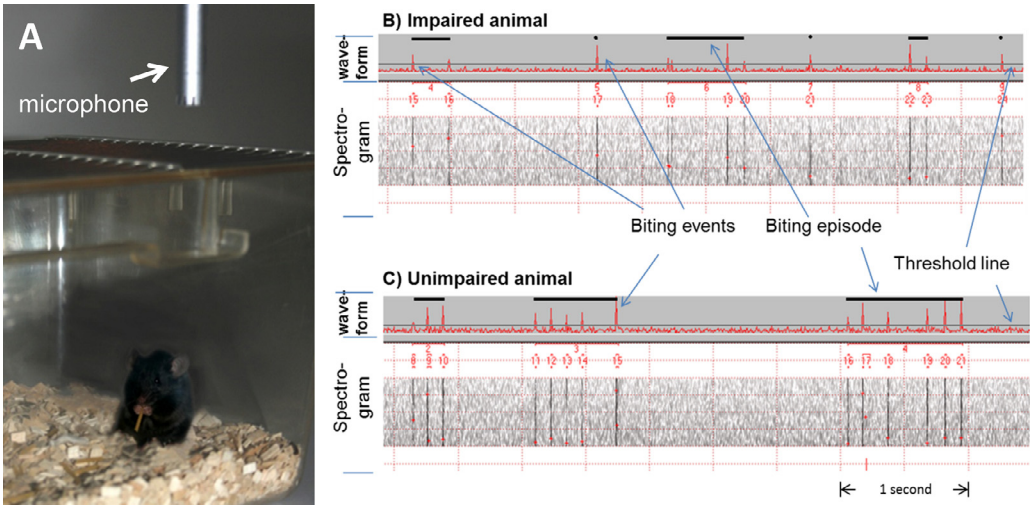

Fig. 1. Experimental setup and readout of the pasta gnawing test. Experimental setup with mouse in home cage and microphone placed close to the wire lid (A). Exemplary biting pattern of an impaired (B) and an unimpaired (C) animal. Arrows mark biting events, a biting episode and the threshold line. Red dots mark frequency with highest intensity (not used for evaluation). Time axis is shown in the lower right corner in C. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the perimeter of the lid prevented the mouse from walking off the edge. The latency to fall off the wire lid was measured in seconds. A 90 s cut-off time was used (Chaillet et al., 1983).

2.6. RotaRod

This test assesses motor coordination by placing animals on a rotating rod (four-lane Rota-Rod; Ugo Basile) that runs at a constant or an accelerating speed. If a mouse loses its balance and falls onto an underlying platform, the rod automatically stops and records the latency to fall as well as the speed at fall. Prior to the first test session, mice were habituated to the testing system until they were able to stay on the rod at a constant speed of 2 rpm for approximately one minute. During testing, each animal was exposed to the apparatus two times for 180 s per trial. The initial speed of the RotaRod increased from 2 rpm to 20 rpm over an accelerating time of 180 s. When the mice fell, the session was over and the Ugo Basile program stopped the timer (Dunham and Miya, 1957).

2.7. Statistics

Data analysis and graphs were created in GraphPad Prism® 4.03 (GraphPad Software, Inc., CA). Graphs include group means and standard error of the mean (SEM). The significance level was set at $p < 0.05$. All data were tested for normal distribution using the Kolmogorov Smirnov test. Group means of all tests were compared by Two-way ANOVA followed by Bonferroni's multiple comparison test. Due to not normally distributed wire suspension data (Figs. 2 D, 3 D, 4 D), these data sets were additionally analyzed by Wilcoxon Signed Rank test. As hypothetical value the mean hanging time of each transgenic group was used and compared to the mean hanging time of ntg animals of the same age. If not otherwise stated both statistical tests resulted in the same significance. Exact sample numbers are given in the figure legends.

3. Results

3.1. Motor deficits of Line 61 mice

Line 61 mice showed progressive motor impairments starting at 3 months of age compared to ntg littermates in terms of biting peaks per episode (Fig. 2B) in the pasta gnawing test. Analysis of the biting speed in the pasta gnawing test resulted in no significant differences but a trend towards a decreased biting speed in Line 61 mice could be observed (Fig. 2A). Already at 2 months of age Line 61 mice showed highly significant differences in the latency to fall off the RotaRod (Fig. 2C) and the wire in the wire suspension test (Fig. 2D). The onset of motor deficits in Line 61 mice is thus comparable with already published results (Chesselet et al., 2012; Fleming et al., 2004).

3.2. Motor deficits of TAR6/6 mice

TAR6/6 mice showed first motor impairments in the pasta gnawing test at the age of 20 weeks compared to ntg littermates. Significant differences could be observed in the number of biting peaks per episode (Fig. 3B) but not in the biting speed (Fig. 3A). At 6 weeks of age a trend was already obvious in both parameters, but differences were not significant. Similar results were obtained using the RotaRod test (Fig. 3C). Evaluation of the wire suspension time resulted in highly significant differences already at the age of 6 weeks that did not alter over age (Fig. 3D). The onset of motor deficits in TAR6/6 mice is thus even slightly earlier as previously published (Wils et al., 2010).

3.3. Motor deficits of NPC1$^{-/-}$ mice

NPC1$^{-/-}$ mice showed first motor impairments in the pasta gnawing test at the age of 8 weeks compared to wildtype animals. Significant differences could be observed in the number of biting peaks per episode (Fig. 4B) but not in the biting speed (Fig. 4A). Similar results were obtained using the RotaRod test (Fig. 4C). The wire suspension time of NPC1$^{-/-}$ was not affected (Fig. 4D). The onset of motor deficits in NPC1$^{-/-}$ mice is thus comparable with already published results (Voikar et al., 2002; Zhang et al., 2004).

4. Discussion

Our results show, that the pasta gnawing test can detect orofacial motor disturbances in mouse models of various neurodegenerative diseases similar to conventional limb motor tests. The sensitivity of the pasta gnawing test strongly depends on the analyzed parameter, since the analysis of the biting speed only showed significant differences in older TAR6/6 mice. Additionally, the sen-

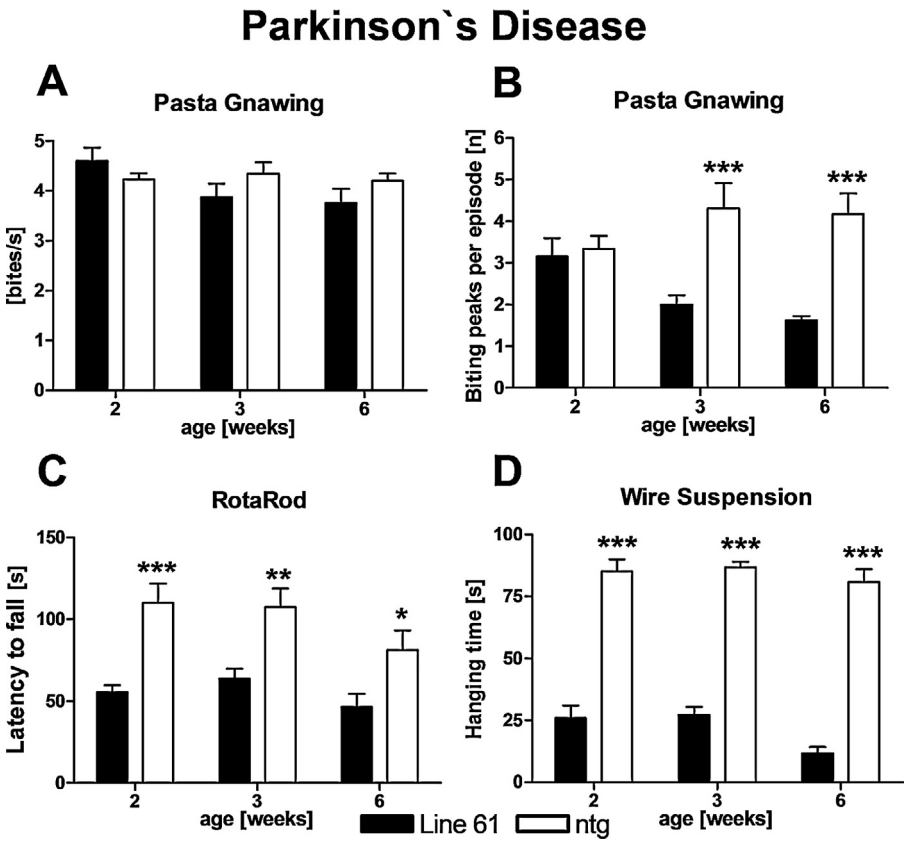

Fig. 2. Evaluation of motor deficits in Line 61 transgenic mice. Biting speed (A) and biting peaks per episode (B) of Line 61 male animals in the pasta gnawing test compared to ntg littermates as well as latency to fall off the Rotarod (C) and wire suspension time (D) of the same animals. n = 10–15/group; A–D: Two-way ANOVA followed by Bonferroni *posthoc* test; D: Wilcoxon Signed Rank test; *p < 0.05; **p < 0.01; ***p < 0.001.

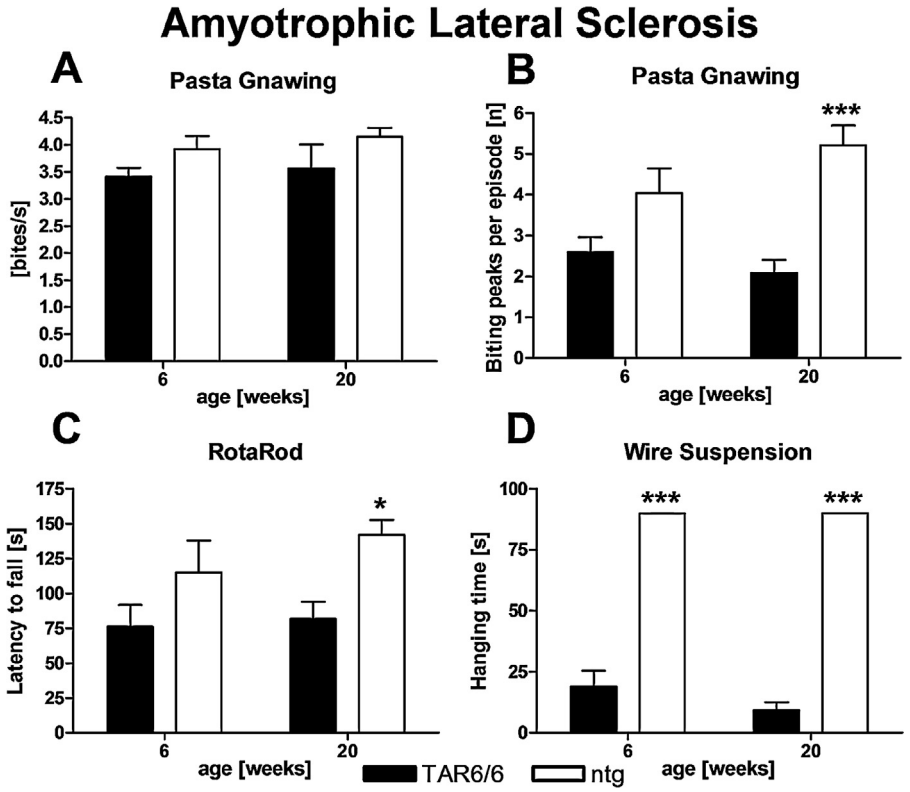

Fig. 3. Motor evaluation of TAR6/6 transgenic mice. Biting speed (A) and biting peaks per episode (B) of TAR6/6 animals in the pasta gnawing test compared to ntg littermates as well as latency to fall off the RotaRod (C) and wire suspension time (D) of the same animals. n = 5–16/group; A–D: Two-way ANOVA followed by Bonferroni *posthoc* test; D: Wilcoxon Signed Rank test; * p < 0.05; ***p < 0.001.

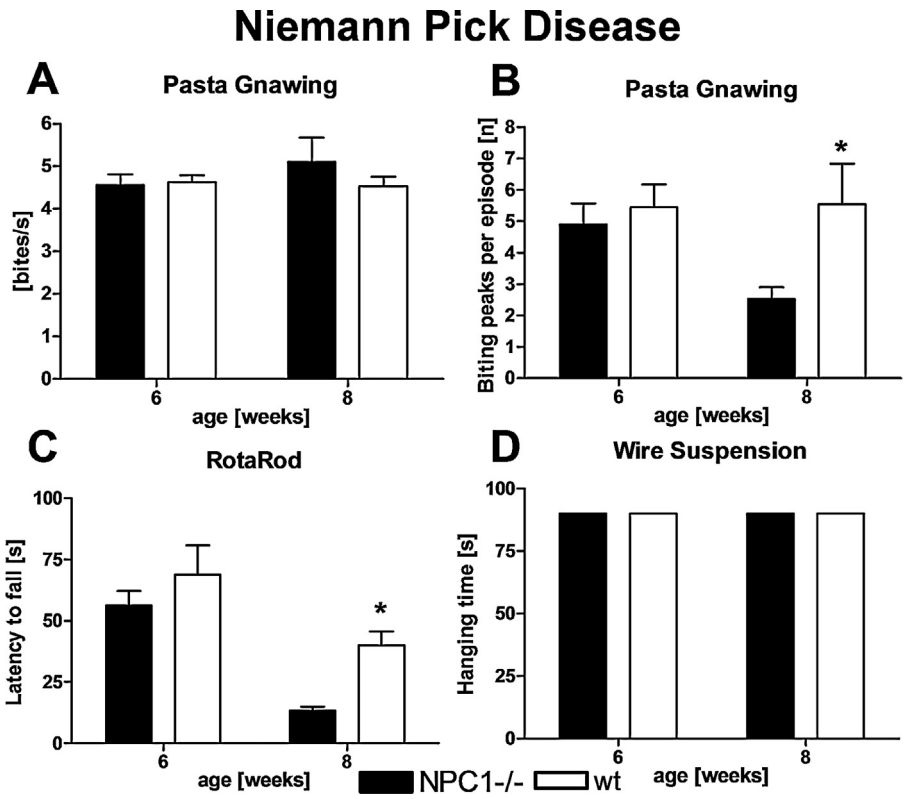

Fig. 4. Motor evaluation of NPC1$^{-/-}$ mice. Biting speed (A) and biting peaks per episode (B) of NPC1$^{-/-}$ animals compared to wt littermates as well as latency to fall off the RotaRod (C) and wire suspension time (D) of the same animals. n = 9-12/group; Two-way ANOVA followed by Bonferroni *posthoc* test; D: Wilcoxon Signed Rank test; *p < 0.05.

sitivity of the test parameter 'biting peaks per episode' depended on the analyzed mouse model. While the sensitivity of the pasta gnawing test compared to the RotaRod was lower in Line 61 mice, it was similar in TAR6/6 and NPC1$^{-/-}$ mice. The sensitivity of the pasta gnawing test compared to the wire suspension test strongly differed between animal models. In the PD model Line 61 and the ALS mouse model TAR6/6 the wire hanging test was able to measure very early deficits, while the pasta gnawing test detected first orofacial disturbances much later, at week 12 and 20, respectively. By contrast, in the NPC1 mouse model the pasta gnawing test detected motor deficits at the age of 8 weeks, similar to the RotaRod, but earlier than the wire suspension test, which did not show any muscle strength alterations in NPC1$^{-/-}$ mice. The onset of orofacial motor deficits of all three transgenic mouse models are thus measurable either at the same time (NPC1$^{-/-}$) or later (Line 61, TAR6/6) than limb motor and muscle strength deficits. The method is thus particularly valuable to analyze the onset of biting deficits in animal models with a very early onset of limb motor or muscle strength deficits, where it is not or hardly possible to analyze the progression of such deficits. The pasta gnawing test is additionally very useful for repeated motor measurements, since the learning bias of this voluntary test should be very low due to the nature of this fundamental motor behavior.

Comparing the onset of deficits observed with the pasta gnawing test in the different mouse models to the human diseases symptoms, a great similarity can be observed. In Line 61 mice, a delayed onset of orofacial deficits compared to limb motor tests can be observed, fitting to the late onset of orofacial dysfunctions in human PD patients (Bakke et al., 2011). In NPC1$^{-/-}$ and TAR6/6 the onset of orofacial symptoms occurs simultaneously or even earlier than the onset of limb motor symptoms and therefore represents an early disease event similar to the symptoms onset in the human diseases (Garver et al., 2007; Murono et al., 2015). Our results thus translate well to the orofacial deficit onset observed in human PD, ALS and NPC1 patients.

In previous studies, a comparable method was used to analyze orofacial deficits in PD rat models. Rats were analyzed for biting deficits after 6-OHDA lesion and the 'mean time to consume the pasta' and the 'mean biting strength' was measured (Kane et al., 2011). In another 6-OHDA rat study, also the 'mean inter-bite duration' was analyzed (Plowman et al., 2013) that is identical to the 'biting speed' shown in our experiments. In a last study characterizing a PINK1 knockout rat, researchers analyzed the 'bite intensity' and the 'inter-bite regularity' (Grant et al., 2015). Here we analyzed the 'biting speed' defined as bites per second. In our study, mice that were only starved for 2 h did not eat the whole pasta piece at once, thus stopping in between. The 'biting speed' did only change in TAR6/6 mice, suggesting that this parameter is rarely changed in transgenic mouse models of motor diseases. The analysis of the 'number of biting peaks per episode' on the other side seems to be a valuable parameter to analyze orofacial motor deficits in different disease mouse models. Another parameter that might be worth analyzing is the 'biting strength', by analyzing the mean amplitude of the biting events (Kane et al., 2011). This parameter might be of particular interest in TAR6/6 mice, since it is shown in ALS patients that dysarthria and dysphagia strongly depend on muscle weakness that would influence the biting strength (DePaul et al., 1988). The measurement of the mean amplitude might however be problematic, since each animal can freely move in the home cage during the evaluation and the distance to the microphone and therefore the measured mean amplitude can thus strongly vary between animals. The analysis of the duration to finish a whole pasta piece is in our opinion not a valuable parameter to distinguish biting deficits in mice, since this parameter strongly depends on the appetite of the animal to eat the pasta. Hence several transgenic animal models are shown to demonstrate an altered metabolism, animals might

be, even after overnight starvation, differently motivated to eat the pasta piece. An overnight starvation could enhance the motivation to eat but would increase the stress level of mice, thus being counterproductive for a voluntary, stress–free evaluation. Even though we did not analyze stress levels of the tested animals, it can be safely assumed that the test is stress free, since animals voluntarily eat the pasta, showing no signs of distress. Additionally, it is already shown that animals that are under stress would not eat at all (Coste et al., 2000). Moreover, the animals seem to enjoy eating dry pasta then even without short-time starvation animals prefer the pasta over their standard chow. The stress-free nature of the pasta gnawing test and the analysis of other motor deficits than limb motor or muscle strength qualifies it as alternative motor test in behavioral test batteries.

5. Conclusion

It can be concluded that the pasta gnawing test displays a novel, powerful tool to characterize rodent models of neurodegenerative diseases. Since the pasta gnawing test shows orofacial deficits later compared to limb motor and muscle strength tests in two out of three rodent models, it will be especially useful as an alternative to limb motor tests for the analysis of compound effects but also in early onset disease models, which are often more vulnerable to stress. The test is furthermore remarkably sensitive resulting in robust results and even more important, the voluntary pasta gnawing test causes far less stress compared to the use of other motor tests.

Authors' contributions

RR designed, performed and analyzed behavioral tests and prepared figures, wrote parts of the manuscript and edited the manuscript. AH performed behavioral tests, and edited the manuscript. CB performed and analyzed behavioral tests and edited the manuscript. SF edited figures and wrote main parts of the manuscript. HR conceived and edited the experiments and edited the manuscript. BHP conceived and interpreted experiments and edited the manuscript. All authors read and approved the final manuscript.

Competing interests

RR, AH, SF and BHP are employees of QPS Austria GmbH. The authors declare that they have no other competing interests.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jneumeth.2016.10.006.

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