

These phenotypes can be attributed to alterations in fat metabolism induced by prohibitin deficiency, linking prohibitin functions in mitochondria with cellular metabolism. Prohibitins are consistently upregulated in tumor cells, but their expression is reduced in senescent cells. The low expression of PHB1 and PHB2 in aged muscle stem cells leads to mitochondrial dysfunction, which can be reversed by increasing the availability of the oxidized form of nicotinamide dinucleotide (NAD⁺). How PHB complexes affect cellular metabolism remains to be defined and it is still a possibility that mitochondrial deficiencies upon loss of prohibitins elicit a general cellular response.

An unexpected function of PHB membrane scaffolds that is independent of their mitochondrial housekeeping function was recently unraveled when analyzing the autophagic removal of damaged mitochondria by mitophagy. PHB2 contains a LC3-interacting domain and can serve as mitophagic receptor in the inner membrane, which ensures the recruitment of the autophagic machinery to mitochondria if the outer membrane is permeabilized.

Do prohibitins have functions outside mitochondria? Several studies have pointed to functions of prohibitins in the nucleus or at the plasma membrane of specific cells. Nuclear prohibitins interact with transcriptional activators and repressors and modulate gene expression. They are also implicated in epigenetic regulation of gene expression in human embryonic stem cells through association with HIRA, a chaperone for histone H3.3. In B cells, platelets and adipose tissues, prohibitins localize to the cell surface where they serve as a receptor for small molecules or play a role in cell–cell communication. Moreover, plasma membrane prohibitins are implicated in infectious diseases. Notably, given their prevalent role in mitochondrial integrity, it remains to be seen whether the function of extra-mitochondrial prohibitins can be dissected completely from their mitochondrial functions. Moreover, the role of hetero-oligomeric PHB complexes has yet to be determined in many of these processes.

Aren't prohibitins good drug targets? Overexpression, altered localization and/or activation by post-translational

modifications (mainly phosphorylation) of prohibitins are all associated with obesity and chemotherapeutic resistance of tumor cells. Pharmacological control of the activity of PHB complexes therefore has great therapeutic potential. Several small molecules exhibiting antitumor effects (e.g. Flavaglines, Aurilide, Melanogenin, Adipotide) target prohibitins, and the efficacy of some of these is currently being tested in clinical trials. Nicotinamide riboside, a precursor of NAD⁺, enhances the self-renewal capacity of muscle stem cells and extends lifespan through prohibitin upregulation in mice. It is envisioned that enhanced activity of PHB complexes augments the health of tissues that are sensitive to mitochondrial integrity in general.

Where can I find out more?

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Primer

Perceptual learning

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Perceptual learning refers to how experience can change the way we perceive sights, sounds, smells, tastes, and touch. Examples abound: music training improves our ability to discern tones; experience with food and wines can refine our pallet (and unfortunately more quickly empty our wallet), and with years of training radiologists learn to save lives by discerning subtle details of images that escape the notice of untrained viewers. We often take perceptual learning for granted, but it has a profound impact on how we perceive the world. In this Primer, I will explain how perceptual learning is transformative in guiding our perceptual processes, how research into perceptual learning provides insight into fundamental mechanisms of learning and brain processes, and how knowledge of perceptual learning can be used to develop more effective training approaches for those requiring expert perceptual skills or those in need of perceptual rehabilitation (such as individuals with poor vision). I will make a case that perceptual learning is ubiquitous, scientifically interesting, and has substantial practical utility to us all.

A practical example: radiology

One of the most often given and easily understandable examples of the practical utility of perceptual learning can be understood in the case of a radiologist, where years of experience and training, with exposure to many thousands of images, is required to achieve expert performance. Radiologists must learn to recognize known anatomy as it is transformed by measurement devices. For example, an x-ray image is the consequence of projecting x-rays through tissue and measuring the relative intensity of the x-rays that emerge. Absorption is essentially a function of tissue density, such that bones absorb more x-rays (showing as light) and soft tissues absorb less (showing as dark). Thus, a possible

Perceptual learning in radiology

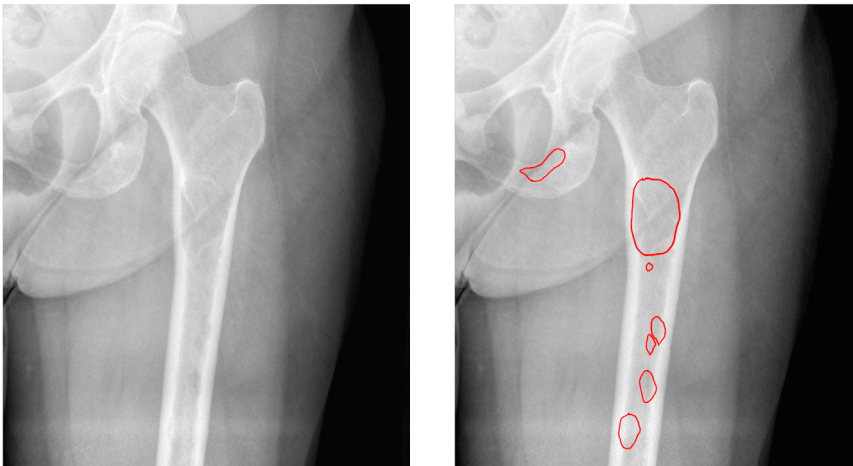


Figure 1. Radiology is hard.

This x-ray image shows a femur bone of a cancer patient with numerous lytic metastases (bone cancer). Test yourself by seeing if you can understand the malignant image features in the circled regions on the right and find them in the image on the left: can you consistently differentiate healthy from diseased tissue?

cancer may show up as lighter than surrounding tissue if it results in an abnormal tissue density or as darker than surrounding bone if it reduces that bone density. But radiologists cannot simply base their diagnoses upon image regions that are lighter or darker than the surround; as each part of the image represents the combined absorption of all tissues along the x-ray path — skin, bones, blood vessels, major airways and possibly organs such as lungs, heart, stomach, liver, and so on — and the contributions of these must all be estimated to make sense of the resultant image.

A first aspect of perceptual learning for radiologists is to develop a vocabulary of image features that relate to normal, benign and malignant properties of the anatomy. Differentiating these image features is crucial to evaluating the health of the patient. To accomplish this, radiologists must estimate the summed absorption of different tissue types and compare this to their knowledge of healthy tissue, while searching for abnormal image features representative of damage or disease. Furthermore, once an abnormality is detected, the radiologist must distinguish between those that are benign (image properties not associated with

negative health outcomes) from those that are malignant (image properties associated with negative health outcomes).

Another key aspect of perceptual learning relates to the fact that interpreting an x-ray requires the discrimination of subtle differences of light and dark that allow extraction of meaningful image features. Radiologists must learn to refine their most basic perceptual skills to quickly and accurately recognize image properties that many individuals can barely recognize even when pointed out. Take a look at [Figure 1](#), showing the x-ray of a femur bone in a cancer patient: can you consistently differentiate healthy from unhealthy tissue in this image? Even with the circled regions it is difficult to see how these differ from other, non-cancerous, regions in the x-ray. Radiology is a good example of the practical utility of perceptual learning, whereby experience can tune our most basic perceptual processes, and is a topic of intense scientific study.

Perceptual learning as a method of sensory calibration

The clearest explanation of the necessity for perceptual learning is in the developing brain's need to calibrate its perceptual systems through interaction with the

environment. The spacing between our eyes, the length of our limbs, in fact most aspects of our body and sensory organs change as we age. Perceptual learning enables our perceptual systems to tune representations of our body and sensory organs and update these representations as we grow. For example, perceptual learning is critical to the development of stereo-vision (requiring knowledge of the spacing between eyes), for coordinating maps of space between visual, auditory and haptic perception (requiring simultaneous inputs from these senses), for learning sounds relevant to our native language, and essentially for tuning all of our perceptual processes during early stages of life.

Much of this early perceptual learning occurs during so-called developmental critical periods shortly after birth when the brain is very plastic, its processes and connections being easily molded by experience. During these critical periods, changes in visual experience can have profound impact on the functional organization of the brain regions responsible for perception. For example, experience is required to develop the appropriate balance of brain territory devoted to each eye and to develop stereo vision by coordinating inputs between the two eyes. In cases of impaired processing in one eye during early development, for example as a result of a juvenile cataract that impairs vision in one eye, the intact eye can take over much of the cortical territory that would normally be shared between the two eyes.

Even when both eyes are normally functioning, if the eyes are misaligned (strabismus), then the brain will often develop a preference for one of the two eyes. This leads to a condition called amblyopia, popularly referred to as 'lazy eye', which can induce a permanent suppression of one of the eyes, which persists even if the ocular misalignment is resolved (either through surgery or use of prism glasses), unless such correction is made in the first few years of life. The fact that correcting a juvenile cataract or strabismus in older children often fails to produce normal vision shows

that perceptual learning significantly diminishes outside of these developmental critical periods.

Similarly, in the acoustic domain, we learn the sound fundamentals of our native language through experience with speech sounds. As a result, we easily recognize sounds that are informative to our native language, but we can experience substantial difficulty hearing some auditory distinctions that are important to foreign languages. A classic example involves the lack of an /r/-/l/ phonetic distinction in native speakers of a number of Asian languages (including Japanese). While Japanese babies can easily distinguish /r/ sounds from /l/ sounds, adult speakers have difficulty (so that they misspeak 'rice' and 'lice'). This perceptual learning, occurring in the first few years of life, allows us to ignore unimportant phonetic distinctions in one's native language in the service of better representing those that are informative. But once this early auditory patterning is complete it is difficult to overcome through adult experience, thus leading to comprehension and pronunciation difficulties in adults attempting to learn a new language.

Adult perceptual learning

In adults, perceptual learning is diminished but not lost, and with proper training adults exhibit an impressive degree of perceptual learning. For example, radiologists, sommeliers, and other 'perceptual experts' master their trade as adults. Thousands of studies of perceptual learning have been carried out in adults, ranging from studies of the most basic perceptual tasks — the quietest sounds that you can hear, the faintest light you can detect, your ability to distinguish different odors, and so on — to studies on complex abilities such as distinguishing faces and figures, interactions between multiple sensory systems, and how perceptual learning manifests in complex real world tasks such as radiology, wine-tasting, and sports. Data show that the adult brain is capable of some improvement in just about any perceptual ability that has been studied. This research addresses what is learned through

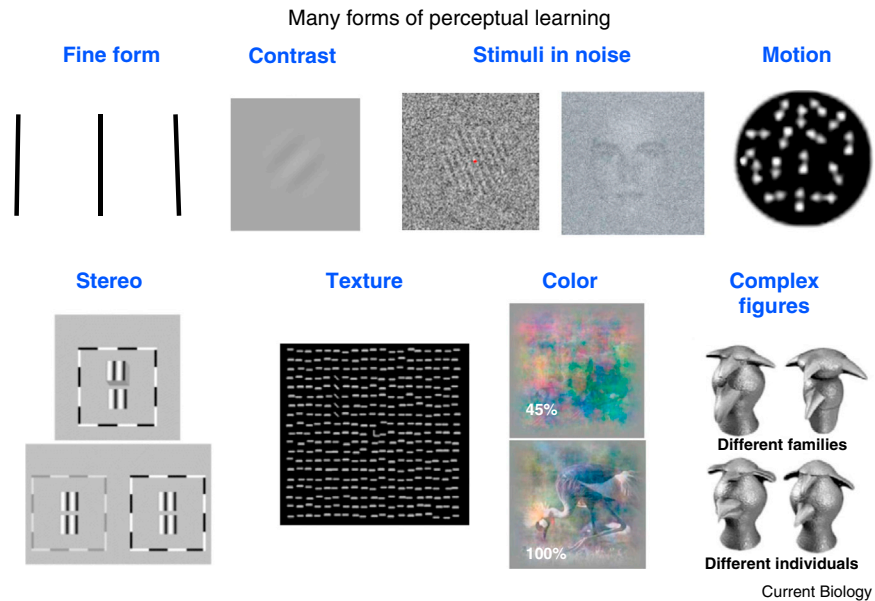


Figure 2. Examples of stimuli characteristic of visual perceptual learning research.

Tasks range from judgments of fine stimulus form, such as 'is the middle line to the left or right of the center of the other two lines?' or 'which of the three lines is tilted?', to detecting subtle patterns of low contrast, discriminating subtle motion directions or textures, for example 'can you find the vertical texture made by five tilted lines?', or learning to discriminate collections of complex figures where categories are defined by multiple features.

perceptual learning, and when and how perceptual learning occurs, with increasing focus on what changes occur in the brain through perceptual learning. In addition to yielding basic knowledge of perceptual processes and brain plasticity, perceptual learning suggests rehabilitation strategies for those with poor vision, such as the case of amblyopia.

Examples of stimuli that are typically used in visual perceptual learning research are shown in Figure 2. Most studies choose a feature of interest — line bisection, orientation discrimination, finding stimuli in noise, motion discrimination, discriminating colors, textures or complex objects, and so on — and train with difficult exemplars for an extended time-period, typically days to months, although some studies have examined fast learning over the time-course of seconds to minutes. Many studies have used adaptive procedures that ensure that performance is maintained at a threshold level of performance where the participant can barely perform the task (typically targeting 75–85% accuracy) for the duration of training. For example, in the case of fine form

discrimination (Figure 2, upper left) this might involve indicating whether a line is straight or tilted (for example, the third line has a slight tilt). This task can be particularly difficult when the stimulus is briefly presented in your peripheral vision. Research shows that an untrained participant may have threshold performance in the range 6–15 degrees of rotation to perform this task accurately. With training of a week or two, humans can often achieve thresholds of 2–4 degrees of rotation, while monkeys that are trained for many months have been shown to reach thresholds of less than 1 degree. The extent of perceptual learning ranges considerably depending upon the amount of training and the particulars of the trained skills, but with extensive training even basic perceptual skills can improve considerably. The primary result of most perceptual learning research is that performance thresholds improve with time, so that by the end of training participants can accurately discriminate stimuli that would have been indistinguishable to them at the onset of training.

While it is well established that perceptual learning is an

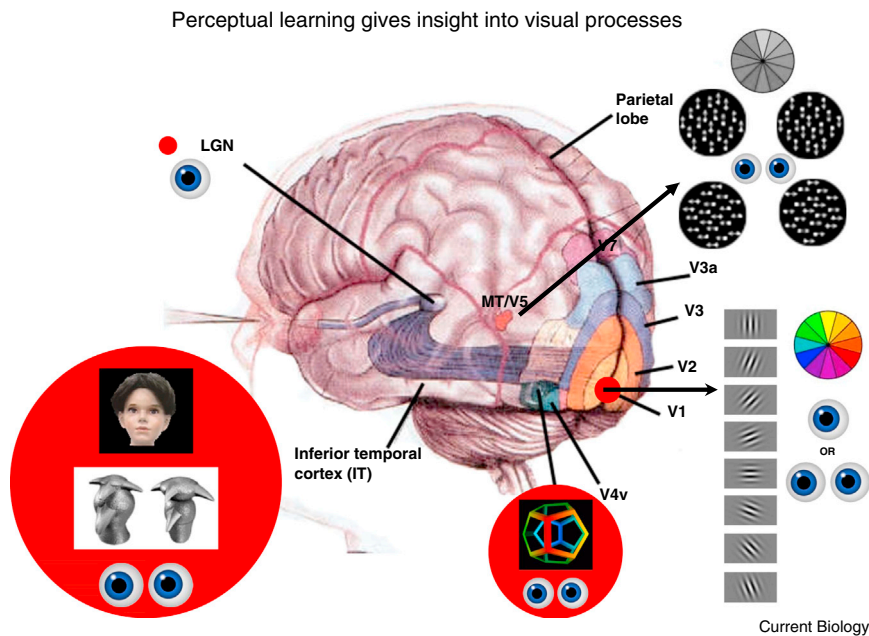


Figure 3. Cartoon illustration of different feature selectivities exhibited by different visual brain areas.

Neurons in the LGN respond to a small area of the visual field from a single eye (as shown by small red circle and single eye-ball). Neurons in area V1 respond selectively to different orientations and colors and some respond to one eye and others to both eyes. Neurons in area V4 also respond to color and line orientations, but almost all of its neurons are binocular and many respond selectively to three-dimensional forms. Neurons in Inferior Temporal (IT) cortex show selectivity to complex three-dimensional forms such as faces, tools, and other complex objects. With training, neurons in IT can respond to novel complex forms such as those shown above. Neurons in Middle Temporal (MT) cortex and in visual areas of the Parietal Lobe respond selectively to different motion patterns but show poor selectivity to color. Notably, upward of 40 distinct visual processing areas have been identified and each has a unique selectivity to visual features and likely plays a unique role in contributing to perceptual learning.

ubiquitous process in the adult brain, it is typically slow, and can require specialized training. Robust perceptual learning can require tens of thousands of trials of practice and this extensive training sometimes will fail to produce learning. Evidence suggests that mere exposure to visual stimuli can lead to perceptual learning but is often insufficient to yield robust learning. Most research shows that additional factors, such as attention and reinforcement, are needed to produce robust learning. For example, if you are simply exposed to those tilted lines in Figure 2, then perceptual learning will at most be minimal, but if you attend those stimuli while performing a task, you will learn substantially more. Likewise, if you receive feedback on your task that reinforces your accurate responses, this can further improve learning. Interestingly, in some cases perceptual learning can occur even

for stimuli that you are unaware of when those are systematically paired with rewards. The factors — amount of exposure, strength of exposure, relation to attention and reinforcement, interactions of multiple sensory systems in perceptual learning, and so on — that promote perceptual learning, and the underlying brain mechanisms that relate to these factors, are among the most active targets of research into perceptual learning.

While showing performance on the training task demonstrates that a particular visual skill can improve with training, most researchers are interested in the attributes of what is learned. For example, does training on that orientation threshold task give rise to improvements on other visual tasks — that is, does the learning *transfer*? Typically, the answer is no, and in fact perceptual learning can be exquisitely specific to the stimuli

that are trained. For example, in the case of fine orientation discrimination, perceptual learning can be specific to the orientation of the line used during training — for example, rotate the line 90 degrees and training starts over — the location on the retina that the stimulus was projected during training, and even the eye that experienced the stimulus during training.

This hyperspecificity to the characteristics of the training stimuli has been a source of fascination in the field and has led to conjectures of what brain mechanisms are responsible for such specific learning (of primary interest to those interested in brain mechanisms of perceptual learning) and what factors induce learning that is more or less specific (of primary interest to those interested in clinical application of perceptual learning). Notably, perceptual learning is not always specific to the trained features, and cases where perceptual learning generalizes are discussed below in the context of rehabilitation and training.

Perceptual learning as a tool to understand brain representations

The sometimes exquisite specificity of perceptual learning provides clues into the brain regions responsible for the learning. Figure 3 shows a simplified portrayal of how different brain regions show selective responses to different visual features. Retinal ganglion cells from each eye project to the lateral geniculate nucleus (LGN) of the thalamus, which is the earliest stage of visual processing that has been implicated in perceptual learning. Here each neuron responds to inputs from as few as a single retinal ganglion cell and thus selectively reacts to light projected within a tiny region of a single eye. In turn, these LGN cells project to the primary visual cortex (V1) at the back of the head, where individual neurons respond only to inputs from a small region of a single eye. Furthermore, neurons in V1 present oriented receptive fields, selectively responding to a narrow range of line orientations. These selective response patterns have led researchers to conclude

that the orientation, location and eye specificity observed in perceptual learning may be due to plasticity occurring in V1.

Outside of V1, neurons typically respond to stimulation across a larger area of the retina and integrate inputs across both eyes. Many brain regions have been characterized in regard to their visual response properties: for example, neurons in the Middle Temporal cortex (MT) respond selectively to motion but are largely color blind; neurons in Visual Area 4 (V4) respond selectively to three-dimensional forms and color; and neurons in Inferior Temporal cortex respond selectively to faces, tools, and other complex objects. Given these known patterns of selective visual processing in different brain regions, a perceptual learning effect that is specific to motion but not color may imply plasticity in MT, whereas one that is specific to color and three-dimensional form may involve plasticity in V4. Such causal inference is far from certain (and theoretical models do show that this specificity can often be accounted for in brain regions involved in decision making rather than perceptual representation); however, a number of physiological studies in animals and functional imaging studies in humans do provide support for the hypothesis that different brain areas involved in visual processing make specific and different contributions to perceptual learning.

Perceptual learning research has motivated theoretical models that help us understand numerous computational issues related to how perceptual learning may form in the brain. For example, the most basic issue is the stability–plasticity dilemma: how can a system learn new information without overwriting what is already known? The reduction in brain plasticity after developmental critical periods is consistent with the need for the brain to maintain existing perceptual representations once they are formed. Computational models are key to understanding the complex and diverse findings in the field and give insight into what aspects of training give rise to learning that is specific *versus* that which transfers, and what brain (or computational)

systems might be responsible for these different aspects of learning.

Perceptual learning as a tool of rehabilitation and training

While specificity to training features is a gift to those studying the brain processes underlying learning, it is a curse to those looking to use perceptual learning as a training tool. Imagine that you visit an ophthalmologist looking to improve your vision and (s)he says: “well with a month of training I can make you see vertically tilted stimuli better when they are presented within a small region in the periphery of your left eye.” This would be equally unhelpful to the radiologist or the patient with low vision (although some athletes do have visual-field-specific deficits that impact their performance and may indeed benefit from such an approach). Fortunately, researchers have identified many conditions where training can also generalize to untrained stimuli and tasks.

There are numerous factors that contribute to the degree to which a given training approach produces specific learning; examples include the amount of training, the difficulty/precision of the stimulus judgments in training, the interleaving of different stimuli and tasks, and so on. Perhaps the simplest method of promoting generalization of learning is to employ a diverse stimulus set. While training with a single stimulus feature often produces specificity, training with multiple stimulus features — for example multiple line orientations at multiple locations and in both eyes — often produces learning that transfers beyond the training set. This makes sense from the standpoint of an intelligent learning system. If you are presented with only a single example, then generalization may not make sense, while if you see many examples, then they may represent a rule.

While the exact brain mechanisms that determine whether learning is specific or transfers are the subject of significant debate, these routes to transfer provide hope for those looking to apply perceptual learning within clinic settings. To date there is substantial research showing that perceptual learning can ameliorate symptoms of amblyopia, and there

is promise that it can help with other visual problems such as presbyopia, macular degeneration, and so on. At the other end of the spectrum, perceptual learning is increasingly being used to train athletes to see better, and promises to help other experts who require exceptional perceptual abilities. While the difficulty of achieving learning that transfers outside of the training context is still a serious issue in the field, as we continue to build knowledge of the brain mechanisms underlying perceptual learning this can be translated into clinical tools that will have increasing effectiveness in providing training benefit that transfers to daily activities that rely upon good perceptual skills.

Related phenomena

There are numerous phenomena that are related to, and that can sometimes be confused with, perceptual learning. For example, adaptation, priming, statistical learning, perceptual memory, and so on, are all phenomena where experience with perceptual stimuli gives rise to a change in performance when those stimuli are subsequently experienced. Adaptation is often distinguished from perceptual learning by the way that adaptation is a temporary state that regresses back to the unadapted state. There are, however, examples of long-term adaptation, such as the McCulloch effect, where exposure to oriented-colored lines can give rise to a color afterimage that can be stable (under the right viewing conditions, a year later), and these blur the distinction between adaptation and perceptual learning. In many cases the label for perceptual phenomena is based upon the perspective of the researcher, rather than the true underlying brain mechanisms, and thus while it is useful to distinguish between different perceptual processes, the extent to which these processes are truly distinct is an area of open research.

Conclusion

Perceptual learning is an ubiquitous phenomenon that shapes the developing brain and refines perceptual processes throughout our lives. The study of perceptual learning has

produced a rich literature describing the behavioral changes, computational principles and neural structures that underlie this learning. Applying this mechanistic insight of perceptual learning has substantial potential to promote more effective training for those striving to improve their perceptual skills. While to date our knowledge of perceptual learning is substantial, research in the field is active with many unresolved questions and much knowledge still to be gained.

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A hydrodynamically active flipper-stroke in humpback whales

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A central paradigm of aquatic locomotion is that cetaceans use fluke strokes to power their swimming while relying on lift and torque generated by the flippers to perform maneuvers such as rolls, pitch changes and turns [1]. Compared to other cetaceans, humpback whales (*Megaptera novaeangliae*) have disproportionately large flippers with added structural features to aid in hydrodynamic performance [2,3]. Humpbacks use acrobatic lunging maneuvers to attack dense aggregations of krill or small fish, and their large flippers are thought to increase their maneuverability and thus their ability to capture prey. Immediately before opening their mouths, humpbacks will often rapidly move their flippers, and it has been hypothesized that this movement is used to corral prey [4,5] or to generate an upward pitching moment to counteract the torque caused by rapid water engulfment [6]. Here, we demonstrate an additional function for the rapid flipper movement during lunge feeding: the flippers are flapped using a complex, hydrodynamically active stroke to generate lift and increase propulsive thrust. We estimate that humpback flipper-strokes are capable of producing large forward oriented forces, which may be used to enhance lunge feeding performance. This behavior is the first observation of a lift-generating flipper-stroke for propulsion cetaceans and provides an additional function for the uniquely shaped humpback whale flipper.

We deployed suction-cup attached digital recording tags outfitted with high-resolution cameras [7] on krill-feeding humpback whales gathered in large aggregations off the coast of South Africa. We recorded two instances of hydrodynamically active flipper-strokes, performed by different humpback whales (Figure 1A–J; Movie S1, Movie S2). For a flipper-stroke to be hydrodynamically active, it must generate lift and

lift-induced drag as a result of its flapping motion and we used the following visual cues to identify these strokes: both flippers moved symmetrically; the flippers were angled into the path of the stroke; the stroke was oriented perpendicular to the body and not aligned with the direction of travel; there was a clearly visible flipper tip reversal between upstroke and downstroke; and the flipper-stroke occurred rapidly. We chose these criteria because they suggest the flippers are producing lift as a result of the stroke. Specifically, a rapidly revolving hydrofoil angled into the path of motion produces lift, and the orientation of the stroke suggests the lift is directed anteriorly [8]. Also, the symmetrical strokes indicate that the flippers are not being used to perform rolling or turning maneuvers, and the tip reversal suggests that the upstroke is hydrodynamically active and is not the type of recovery stroke that characterizes rowing motions. Finally, the rapid upstroke and downstroke further distinguish our observations from previously documented, drag-based rowing and sculling behaviors [5]. A flipper-stroke does not need to meet all of these criteria to produce lift and drag, and it is possible that further kinematic analysis of common flipper movements will reveal that they also generate hydrodynamic forces. To estimate the forces generated by both flapping humpback whale flippers we used a simple hydrodynamic model based on the blade element theory for flapping appendages (Figure 1K; Supplemental information; [8]). The model assumes that a flapping hydrofoil acts like a propeller blade, revolving in a flat plane with a uniform angle of attack and no translational velocity (Figure 1L).

Our first example of a lift-generating flipper-stroke shows a humpback whale performing a feeding lunge while swimming past the tagged animal (Figure 1A–J, Movie S1). Both the upstroke and the downstroke took 0.8 seconds and had a stroke amplitude of approximately 90° (Figure 1K). The flipper-stroke was oriented perpendicularly to the body. Assuming the flipper is 4.16 m long [3], the average velocity of the flipper tip is calculated as 8.2 m/s. The radius of gyration of the humpback flipper is 2.26 m, and the average translational velocity at this radius is 4.4 m/s. Across a range of plausible angles of attack [2], two flapping flippers are capable of producing