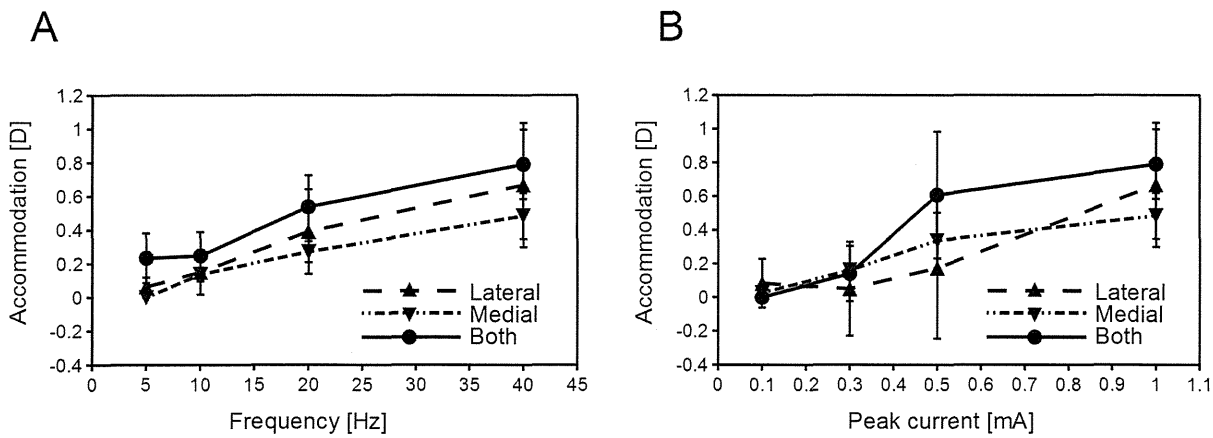

Figure 4. Maximum amplitude of accommodation as a function of the frequency (A) or current (B) of the stimulus. A: The frequency was varied and the current was fixed at 1 mA. B: The current was varied and the frequency was fixed at 40 Hz. One or 2 drops of phenylephrine hydrochloride was instilled prior to the measurements. The maximum amplitude of accommodation is the average of four eyes of four cats (Cat #2, #4, #6, #7). Error bars indicates standard deviations. Monophasic square pulses at a fixed pulse width of 0.5 ms were applied to the lateral, medial, or both branches of the short ciliary nerve.
doi:10.1371/journal.pone.0105615.g004

increasing the currents >1 mA or the frequencies >40 Hz did not increase the amplitude of accommodation significantly. When both branches of the ciliary nerve were stimulated, the accommodative responses were greater than when only one branch was stimulated in 3 of 4 cats.

Dynamic Accommodative Responses

The accommodative responses were obtained by a sequential recording of the wavefront aberrations. The latency of accommodation was always shorter than the detection limit, <100 ms, of our instrument. The accommodation amplitude continued to change during the 4 seconds after the onset of stimulation (Figure 5A). With longer stimulus durations, the amplitude of accommodation reached and maintained a steady state during the stimulation (Figure 5B). After the stimulation, the accommodation decreased slowly to the original level within 10 sec.

The velocity of accommodation varied among the trials. A comparison of the velocities of accommodation and the maximum amplitude of accommodation are shown in Figure 6. The velocities increased significantly with increasing maximum accommodation (Pearson's correlation; $r = 0.839$, $P<0.001$).

Dynamic Pupillary Dilation

The pupil dilated asymmetrically when one branch of the ciliary nerve was stimulated, but if both branches of the ciliary nerve were stimulated, the pupil dilated symmetrically. The pupil never constricted in response to the stimulation parameters used. Representative images of the pupils are shown in Figure 7. The pupillary image before stimulation is shown in Figure 7A. Stimulating the lateral branch (7B) or the medial branch (7C) of the short ciliary nerve produced asymmetric dilation. The pupillary image when both short ciliary nerves were stimulated by the same parameters is shown in Figure 7D.

The time course of the pupillary dilation is shown in Figure 8. The pupil dilated laterally in the case of lateral branch of the short ciliary nerve was stimulated and the pupil dilated medially in the case of medial branch of the short ciliary nerve was stimulated. The pupil dilated symmetrically when both branches were stimulated (n = 2).

Table 1. Maximum accommodative response.

	Maximum Accommodative Response (Diopter)		
No.	**Lateral**	**Medial**	**Both**
#1	1.08	0.88	
#2	0.25	0.46	0.67
#3	1.19	0.30*	
#4	0.80*	0.36*	1.01*
#5	0.58*	0.20*	
#6	0.95*	0.63*	0.60*
#7	0.18*	0.20*	0.41*

Trains of monophasic square pulses were applied to the lateral, medial or both branches of the short ciliary nerve(1 mA, 40 Hz, 8 sec). The maximum accommodative amplitudes were evaluated by the changes in the refractive power.
*: 1 or 2 drops of Phenylephrine Hydrochloride was instilled.
doi:10.1371/journal.pone.0105615.t001

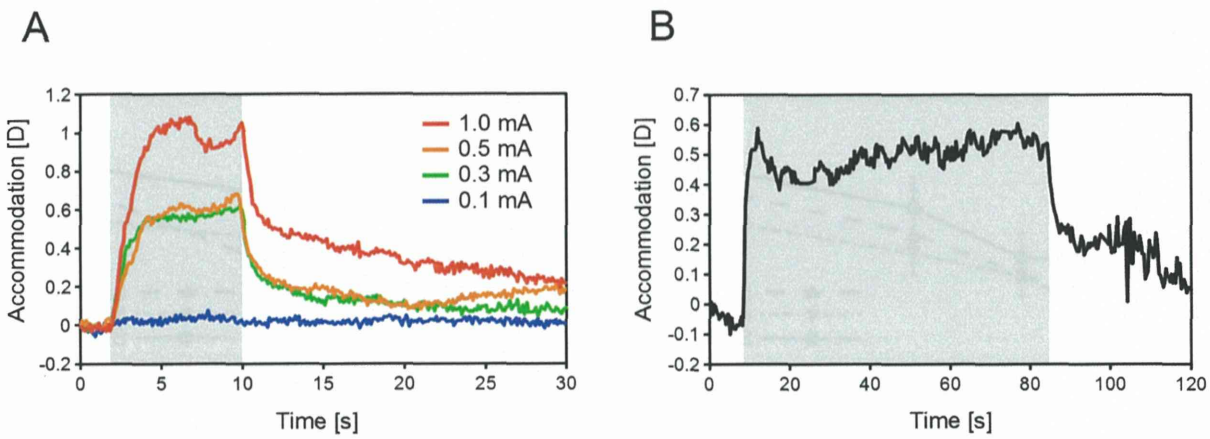

Figure 5. Effect of current and stimulus duration on accommodative responses. A: Typical accommodative responses (Cat #1). Trains of monophasic square pulses of different currents were applied to the lateral branch of the short ciliary nerve. The pulse width and frequency were fixed at 0.5 ms and 40 Hz respectively. B: Efffect of continuous stimulation. A current of 1 mA, frequency of 20 Hz, and duration of pulse train of 75 sec were applied. Shaded areas: Time stimulation was applied.
doi:10.1371/journal.pone.0105615.g005

The latencies of the pupillary responses were always shorter than the detection limit (less than 100 ms). After the stimulation, the pupil gradually returned to the original state within several tens of seconds.

Wavefront Aberrations

The wavefront aberrations changed with accommodation. A typical example of the time course of the Zernike coefficients and accommodative responses are shown in Figure 9. The time courses of changes in Zernike terms were similar to those of the accommodative responses. The averages and standard deviations of the Zernike coefficients in the seven cats are shown in Figure 10. Zernike coefficients up to 6th order can be calculated with our software. However, the 4 to 6th order of the Zernike terms except for spherical aberration term (Z^0_4) are not shown in the results because these terms changed only slightly in almost all trials. The changes of the Zernike coefficients were determined by subtracting the maximum value during the stimulation from the pre-stimulation value. The stimulation parameters were fixed with a peak current of 1 mA, frequency of 40 Hz, and pulse width of 0.5 msec.

We compared the findings between stimulating the lateral and medial branches of the short ciliary nerve. Significant statistical differences were found in the oblique astigmatism term. However, significant statistical differences were not found for all of the other Zernike terms.

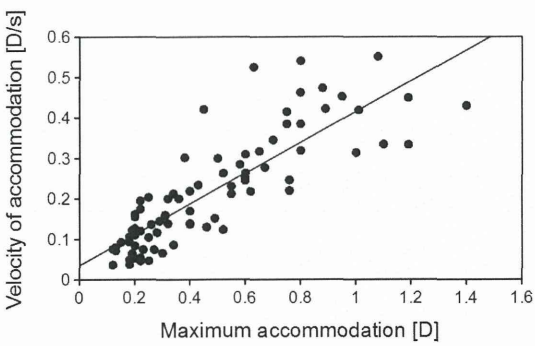

Figure 6. Changes in the velocity of accommodation as a function of maximum accommodation. Stimulus was applied to the lateral or medial or both branches of the ciliary nerve. The data from all seven cats are plotted. Correlations between the velocity of accommodation and maximum accommodation made by Pearson's correlation ($r = 0.839$, $P<0.001$).
doi:10.1371/journal.pone.0105615.g006

Discussion

Our results showed that stimulation of the short ciliary nerve leads to simultaneous changes in the accommodation, pupillary diameter, and wavefront aberrations. The pupil was never constricted during the stimulation of the branches of short ciliary nerve. Lens accommodation is under the control of the parasympathetic system, while the pupil is under the control of the sympathetic system. Our findings indicate that the nerve bundles which were stimulated contained both sympathetic and parasympathetic nerve fibers. In fact, Kuchiiwa et al. showed in their anatomical studies that the short and long ciliary nerves fuse close to the eye in both the medial and lateral divisions of the short ciliary nerve [28,29]. The other possible cause of these responses is due to stimulating the sensory nerve in the short ciliary nerve.

The amplitude of accommodation increased with an increase in the frequency and the current of stimulation (Figure 4). The maximum amplitude of accommodation was 1.19 diopters, and increasing the currents >1.0 mA and frequencies >40 Hz did not increase the amplitude of accommodation.

In earlier studies, the maximum accommodation in cats was around 2 diopters when the ciliary ganglion was stimulated [1–3]. In addition, the near point of physiological accommodation in cats was estimated to be between 25 to 36 cm or 2.8 to 4.0 D [30]. The maximum amplitude of accommodation under our conditions was less than these values. This disagreement might be caused by the contact between hook shaped electrodes and nerve bundle, and the hook electrodes placed on the nerve bundle might have stimulated only a part of it.

The latencies of accommodation were always less than the detection limit of our recording system (Figure 5). Earlier studies showed that the latencies were >200 ms in the case of ciliary ganglion or midbrain stimulation in cats [27,31,32]. This

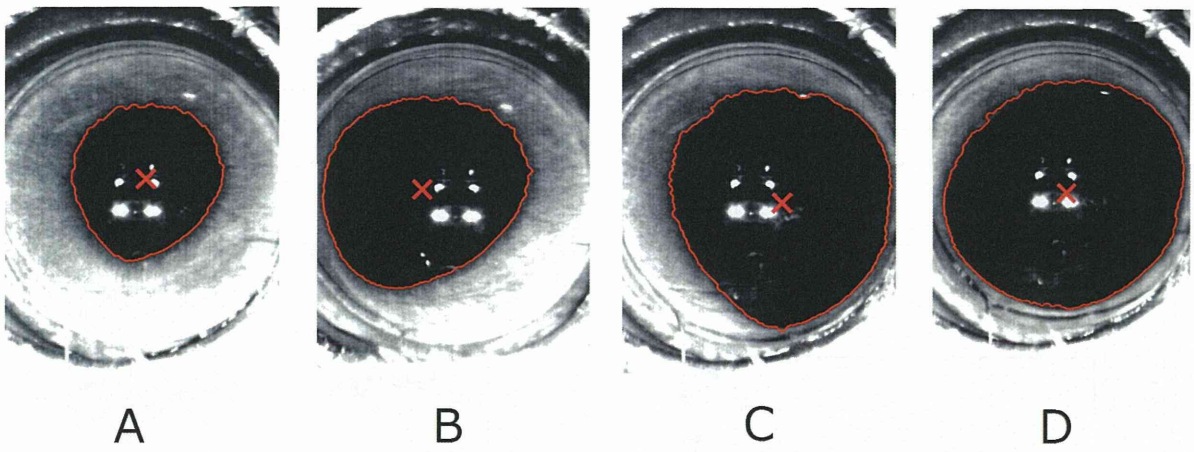

Figure 7. Pupillary images before and after electrical stimulation of the ciliary nerve (Cat #2 right eye). A: Before stimulation. B: Maximum dilation when the lateral branch of the short ciliary nerve was stimulated. C: Maximum dilation when medial branch was stimulated. D: Maximum dilation when both side of branch was simultaneously stimulated. Solid line: Detected contour of the pupil. X: The center of the pupil that is represented as the center of gravity that was calculated from contour data.
doi:10.1371/journal.pone.0105615.g007

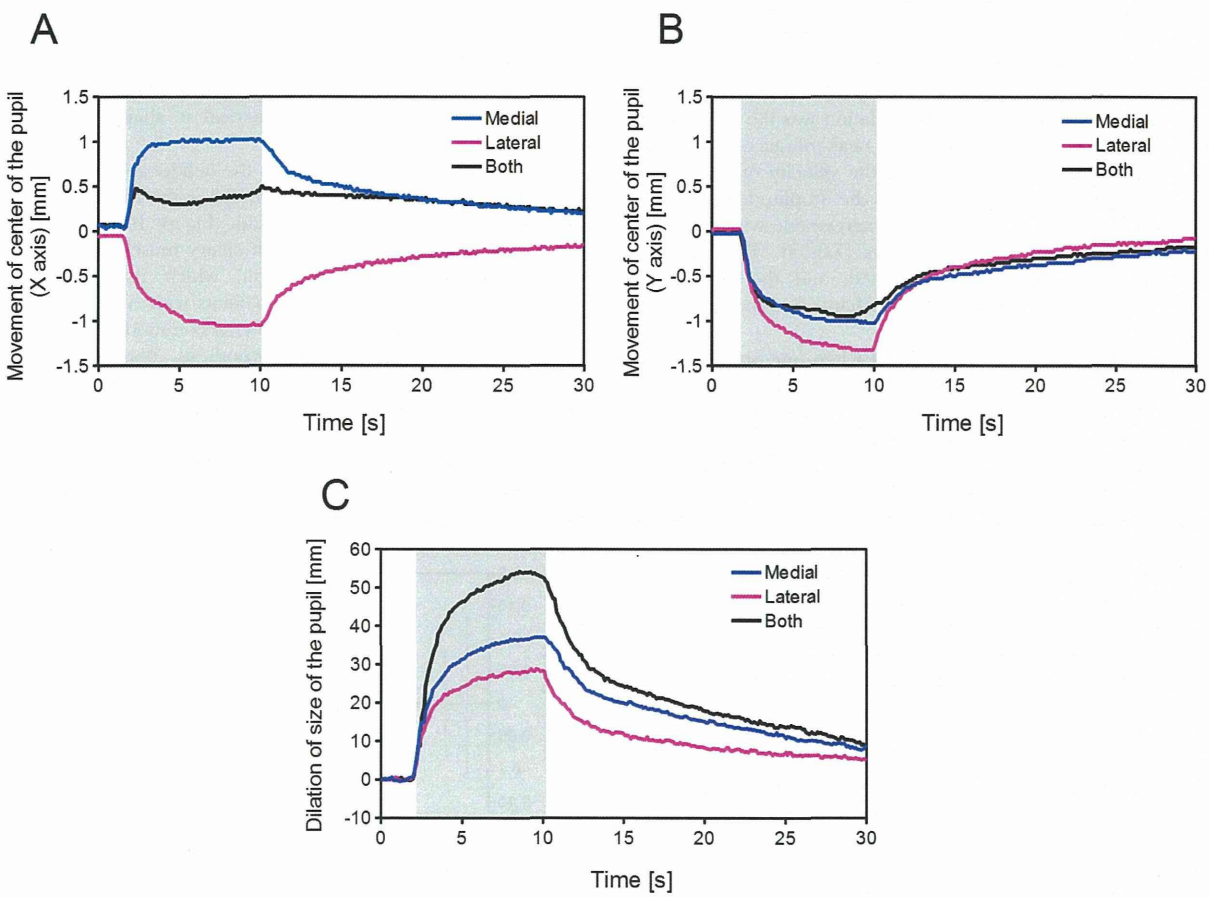

Figure 8. Time course of the changes in the pupillary response to electrical stimulation of one or both branches of the short ciliary nerve (Cat #2). A: Horizontal movement of the center of the pupil. The direction of medial side is represented by positive x-axis, the lateral side is represented by negative x-axis. B: Vertical movement of the center of the pupil. The superior direction is represented by upward dilation, and the inferior direction is represented by downward dilation. C: Changing of the pupil size calculated from the detected contour data. Shaded areas: Stimulation (the pulse train was continuously applied).
doi:10.1371/journal.pone.0105615.g008

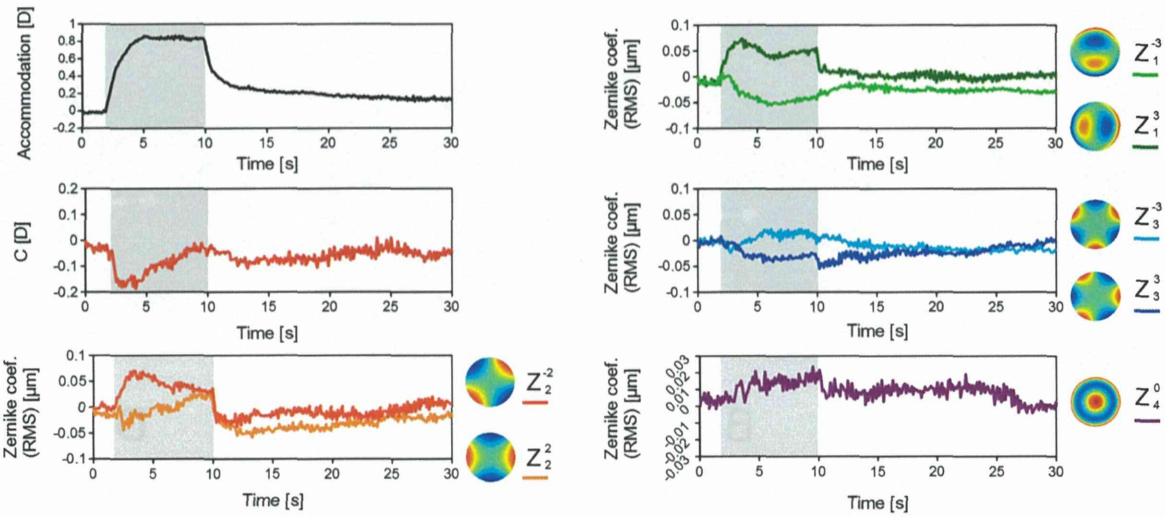

Figure 9. The time course of the changes in the Zernike coefficients and accommodative changes. (Cat #1) S. E.: Spherical Equivalent of refractive change, C: Cylindrical value. All data are the values of the change from the initial state. Shaded areas: Stimulation (the pulse train is continuously applied). The current of 1 mA, the frequency of 40 Hz, the duration of pulse train of 8 seconds were applied to the lateral branch of the short ciliary nerve.
doi:10.1371/journal.pone.0105615.g009

discrepancy might be caused by a difference of the stimulation sites.

The maximum velocity of accommodation was 0.6 D/s in this study taking 4 seconds to reach the peak of accommodation (Figure 4). In addition, we found that the velocity of accommodation was significantly correlated with the amplitude of accommodation (Figure 6). This is in good agreement with previous studies in humans and rhesus monkeys [7,8,33]. The latencies might depend on the region stimulated, and the velocity of accommodation may depend on the mechanical properties of the ciliary body and the crystalline lens.

The pupil was asymmetrically dilated when one branch of the ciliary nerve was stimulated (Figures 7 and 8). This suggests that each branch innervates localized areas of the dilator muscle of the pupil. Asymmetric pupillary dilation indicates that the ciliary muscle may also be asymmetrically constricted by stimulation of the short ciliary nerve on one side. If ciliary muscle constricted asymmetrically, asymmetric terms of wavefront aberrations should be changed.

In all trials, the pupil was dilated or was kept stable in size, but never constricted to any of the stimulation parameters. This might be explained by a concurrent stimulation of both parasympathetic and sympathetic nerve fibers. In cats, the sympathetic fibers are reported to be incorporated in the short ciliary nerves after the nerves have been joined by the long ciliary nerves somewhere between the ciliary ganglion and the eye [34]. At the area of the branch of short ciliary nerve which was stimulated in this study, about 5 mm from sclera, the parasympathetic and sympathetic fibers might be mixed. Our results indicated that the stimulation of mixed sympathetic and parasympathetic fibers will cause a dilation. The discharge rate of the mixed ciliary nerve is increased with spontaneous pupillary dilation in cats [35].

The wavefront aberrations change with accommodation in humans, and the spherical aberration (Z^0_4) shows the greatest change among all the Zernike terms [12]. The changes in the astigmatism and the coma terms were smaller than that for spherical aberration. In contrast, the changes in the spherical aberration was smaller than for the astigmatism and coma terms (Figures 9 and 10). These discrepancies may be due to differences in the shape of the crystalline lens between humans and cats. The crystalline lens of cats is more spherical in shape than that of humans.

The differences in the changes in the oblique astigmatism term (Z^{-2}_2) between stimulation of the lateral or the medial branch of the short ciliary nerve were significant (Figure 10). This suggests that an asymmetrical constriction of ciliary muscle is induced by unilateral ciliary nerve stimulation, which may induce the deformation of crystalline lens. In patients with Adie's syndrome, astigmatism is reportedly induced after accommodation [23]. Our findings in cats support the hypothesis that a segmental constriction of ciliary muscle occurs when patients with Adie's syndrome accommodates which eventually causes the increase of asymmetrical astigmatism.

Further study is necessary to confirm the localized innervation of the short ciliary nerve that lead to the asymmetric contraction of the ciliary muscle. It is also necessary to make a computer

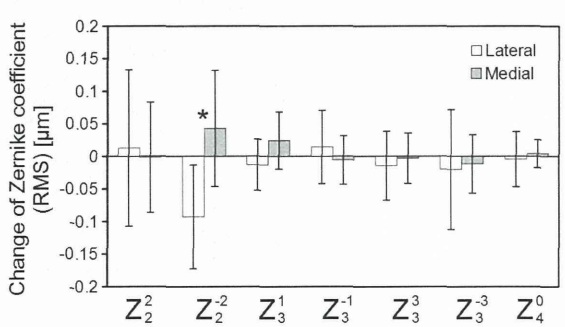

Figure 10. The average change of Zernike coefficients among the seven cats. Error bars represent the standard deviations. A current of 1 mA, frequency of 40 Hz, and duration of pulse train of 8 seconds were applied. Comparisons between the two cases (lateral or medial branch of short ciliary nerve stimulation) were made by Student's *t* tests. The level of statistical significance was set as $P<0.05$. (*: $P<0.05$).
doi:10.1371/journal.pone.0105615.g010

simulation if the asymmetric movement of ciliary muscle induces the deformation of crystalline lens.

In conclusion, we measured the dynamic change of the wavefront aberrations, pupillary size and shape, and accommodation simultaneously and serially with a custom-built compact wavefront aberrometer. The asymmetric pupillary dilation and asymmetrical changes of the wavefront aberrations with accommodation elicited by electrical stimulation on one branch of the ciliary nerve suggest that the branch of ciliary nerve innervates localized regions of the dilator of pupil and ciliary muscle.

Author Contributions

Conceived and designed the experiments: SM HK YH TE TF T. Miyoshi T. Morimoto T. Mihashi. Performed the experiments: SM HK YH TE TF T. Miyoshi. Analyzed the data: SM YH. Contributed reagents/materials/analysis tools: SM HK YH T. Miyoshi. Wrote the paper: SM YH TF.

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特集3

電気信号を用いた神経機能再建

人工網膜 (suprachoroidal-transretinal stimulation: STS)

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SUMMARY

視覚神経系への電気刺激により，視機能を再建する医療機器「人工網膜」の研究開発が進められている．その仕組みは，眼の代わりに眼鏡枠に取り付けた小型カメラで外界の画像を撮影し，画像データを基に刺激電流を生成し，網膜近傍に設置した多極電極を介して網膜を電気刺激することで人工の視覚を作る．すでに臨床試験が各国で行われており，近い将来の実用化が期待されている．わが国では，2001年より大阪大学を中心に人工網膜の開発プロジェクトがスタートし，独自の刺激方式である suprachoroidal-transretinal stimulation (STS) 方式を採用した人工網膜の開発が進められている．現在，第二世代型STS人工網膜が完成し，その臨床試験が実施されている．

KEY WORDS
人工網膜
人工視覚
神経インタフェース
視覚再建

はじめに

網膜への電気刺激により生じる擬似的な光感覚を利用して，人工的に視覚を再建する医療機器「人工網膜」の開発が国内外で進められている．人工網膜の対象は網膜色素変性をはじめとする視細胞が退行変性する網膜変性疾患である．本稿では，著者らが開発を進める suprachoroidal-transretinal stimulation (STS) 方式の人工網膜を中心に，人工網膜のしくみと現在の研究状況について紹介する．

I. 網膜色素変性

人工網膜の主な対象疾患は網膜色素変性である．初期には夜盲を自覚し，視野狭窄および視力低下が徐々に進行し，重度の場合には失明に至ることもある．現在の医療の現場では，治療法は皆無で，わが国における中途失明原因の第三位を占める[1]．

通常，健常な網膜では，網膜に到達した眼内入射光が視細胞で神経信号へと変換され，双極細胞，網膜神経節細胞へと順に伝達される．一方，末期の網膜色素変性の場合，光受容器である視細胞が広範囲に退行性変性するために，眼内入射光を神経信号に変換することができない．しかし病態が進行した場合でも網膜神経節細胞などの網膜内層の神経細胞が残存することが

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知られている[2]．したがって，網膜内層の神経細胞をターゲットとして電気刺激を与えることで同細胞の神経活動を人工的に誘発し，これが視覚中枢に伝わることで擬似的な光感覚「electrical phosphene」が生まれる．

II. 人工網膜の仕組み

人工網膜は，人工的な方法で光を受光し，光を電気信号に変換し，電気信号を網膜内の視細胞以外の神経細胞に伝達して人工的に光感覚を生みだす装置と定義されている[3]．具体的には，カメラで得た外界の画像情報に合わせて網膜近傍に埋植した多極電極で複数のelectrical phosphene を生み出してパターンを作製する（**図 1**）．

世界的にみて，人工網膜の研究が本格的に始まったのは 1990 年代以降である．当初は主にアメリカやドイツの研究グループが中心となり研究を進めていたが，2000 年代に入り日本をはじめオーストラリアや韓国も参入するようになった．

現在までに考案されてきた人工網膜は多極電極の埋植位置によって，網膜上刺激方式，網膜下刺激方式，STS 方式に大別される（**図 2**）．

網膜上刺激方式は多極電極を網膜の上側に設置して網膜を刺激する方式である．この方式の中で最も開発が進んでいるのが Second Sight Medical Products 社（米国）の“Argus Ⅱ”である．これは南カリフォルニア大学の Humayun らの研究が基となって開発された人工網膜である．これまでに 30 名以上の網膜色素変性患者に対して多施設臨床試験が実施された[4]．Argus Ⅱは 2011 年に CE マークを取得し EU 圏内での販売が認められた．さらに 2013 年には米国食品医薬品局（FDA）の認可を受けアメリカ国内での販売が認められた．

網膜下刺激方式は，多極電極を網膜と脈絡膜の間に設置して網膜を刺激する方式である．この方式の中で最も開発が進んでいるのが，Retinal Implant 社（ドイツ）の“Alpha IMS”とよばれる人工網膜である．これはチュービンゲン大学の Zrenner らの研究成果によって開発された人工網膜である[5]．このデバイスには多極電極基板上に 1,500 個の素子が組み込まれ，各素子は受光素子と増幅器と刺激電極で構成されている．これにより多極電極で撮像と電気刺激を同時に行うことができる．これまでの臨床試験で約 20 例の手

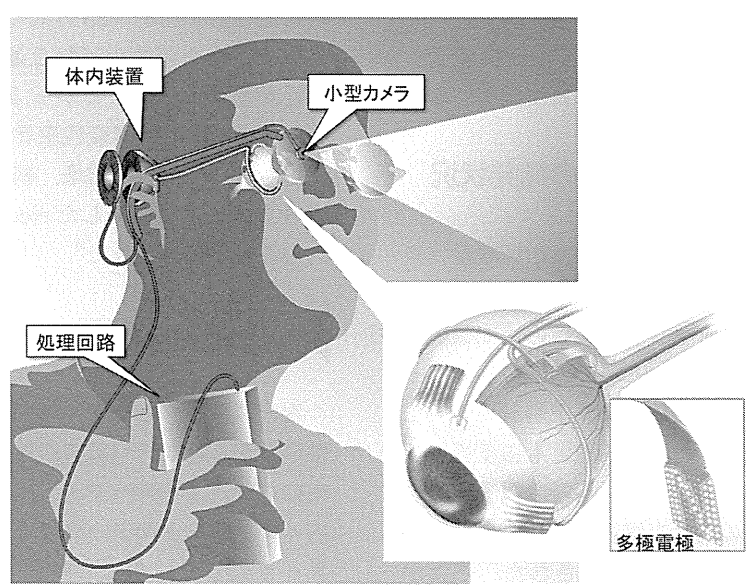

図 1　人工網膜の全体システム
（p.6 カラー図参照）

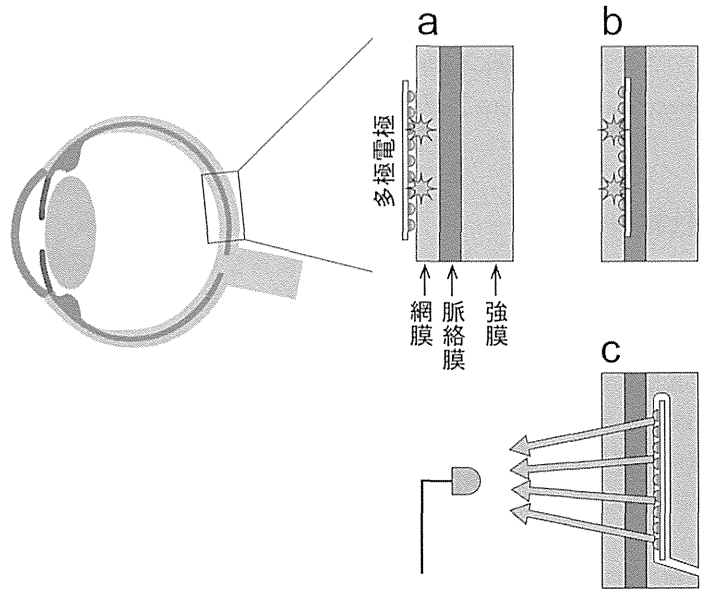

図 2　人工網膜の三つの方式
a：網膜上刺激方式．b：網膜下刺激方式．c：STS 方式．（p.7 カラー図参照）

術が実施された．さらなる臨床試験が，ドイツ，英国，香港などで実施されている．すでに CE マークを取得しており，EU 圏内での販売が認められた．また，米国における販売に向け現在 FDA にて審査が行われている．

STS 方式は多極電極を脈絡膜よりも外側に設置し網膜を刺激する．本方式の詳細は次章にて説明する．

III.　STS 方式の人工網膜の開発状況

わが国では，2001 年度に大阪大学の故田野教授（当時）をグループリーダとして大阪大学，奈良先端科学技術大学院大学，（株）ニデックなど複数の研究機関が参加して人工網膜の開発プロジェクトが立ち上がった．当初は網膜上刺激型あるいは網膜下刺激型の人工網膜の検討が進められていたが，両者ともに多極電極が網膜組織に直接接触するために手術時の網膜損傷のリスクが高い．これらの問題を回避するために，当プロジェクトで新しい刺激方式が考案された．それが STS 方式である．

STS 方式では電極を脈絡膜よりも外側に設置し，帰還電極を硝子体腔中に設置して両電極間で通電する．電極が網膜と直接接触しないため，手術時の網膜損傷のリスクが他の方式よりも低い．ほかにも，網膜への広い範囲に電極を埋植できる点や，再生医療との併用が可能な点が STS 方式の利点としてあげられる．

さまざまな非臨床試験を通じて STS 方式の実現可能性が示された[6,8]ことから，2004 ～ 2008 年にわたり，合計 4 名の網膜色素変性患者に対して急性臨床試験が実施された．試験の結果，網膜色素変性症例に対して STS 方式により限局した electrical phosphene が得られることが確認された[9]．

IV.　第一世代型 STS 方式人工網膜システム

次のステップとして，当プロジェクトは体内への慢性埋植が可能なデバイスの開発に着手した．当時，国内にペースメーカーや人工内耳など電子医療機器の体内インプラントのメーカはなく，開発はゼロからのスタートだった．多くの時間と労力を要したが，2010 年に体内埋植可能なデバイスの試作に成功した．このデバイスには 9 極型の多極電極が搭載された（**図 3**）．

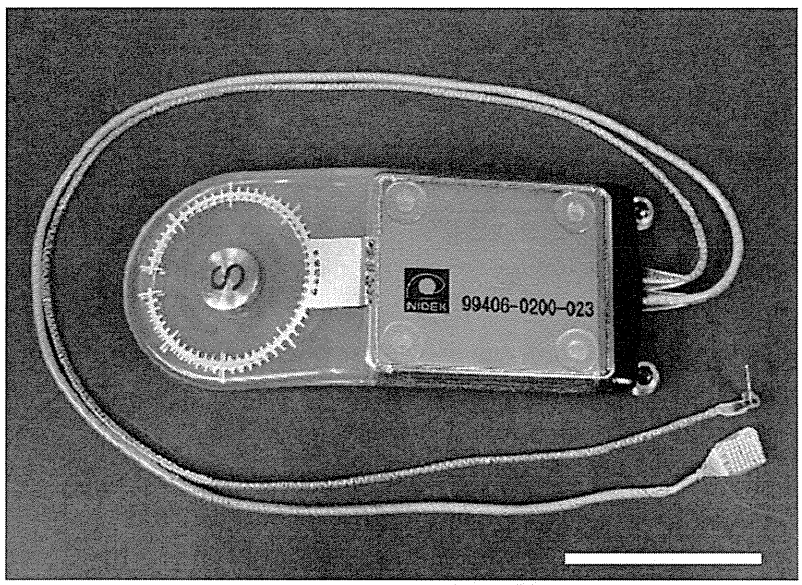

図3　第一世代型STS方式人工網膜の体内装置（スケールバー：3 cm）

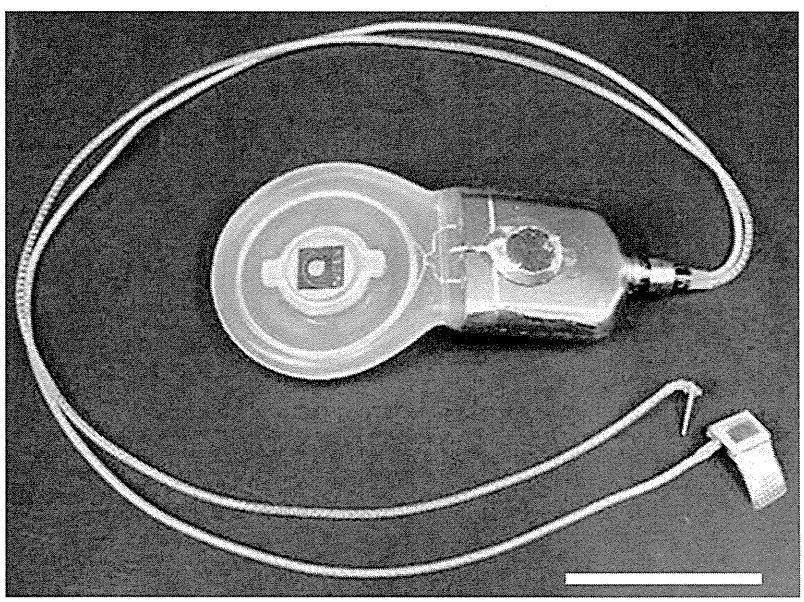

図4　第二世代型STS人工網膜の体内装置（スケールバー：3 cm）

大阪大学医学部倫理委員会の承認を得て，網膜色素変性の患者2名に対して最長1ヵ月半の慢性臨床試験が実施された[10]．機能試験を実施したところ，埋植手術を受けた患者はこの人工網膜を使って眼前に提示した太さの異なる二つの棒を識別できた．なお，デバイスの埋植手術，慢性埋植，そして摘出手術に伴う有害事象は発生しなかった．

V. 第二世代型STS方式人工網膜システム

その後も引き続きデバイス開発は進められた．そして完成したのが第二世代型STS人工網膜システムである．第一世代と第二世代の主な違いは電極数である．第二世代では49極型（7×7の配列）の多極電極が体内装置に搭載された．このほかにも，体内装置本体が第一世代よりも小型化された（**図4**）．大阪大学医学部倫理委員会より埋植期間1年の臨床試験が承認され，現在，3名の網膜色素変性の患者を対象に，同システムの臨床試験が行われている．

おわりに

従来は実現困難と考えられてきた人工網膜であるが，近年の急速な電子技術の進歩や医療材料の進歩により実用化への道が開けてきた．わが国においてもSTS方式人工網膜の臨床試験が進行中で，その有効性と安全性が検証されつつある．近い将来，医療の現場で人工網膜が用いられるようになると思われる．今後は，人工網膜埋植後の患者の視機能リハビリテーションをどのように行っていくか，そして適応患者の選択に要する事前検査方法の確立などについての検討が必要となると考えられる．

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