International Journal of Clinical & Experimental Otolaryngology (IJCEO)
ISSN 2572-732X

Regulation of Voice Development in Childhood and Puberty, A Review

Review Article

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Abstract

Our aim with this systematic review was to get further knowledge of the biological background of the normal human voice production. The search included genetics and brain development related to voice production as well as hormones. Only 18 papers were found in a search made by the library of the Royal English Society of Medicine, We supplemented the systematic search with references, found in papers that did have interesting information even if no voice production measures were found.

Voice analysis included the quantitative GAT (glottal analysis tools), OCT (optical coherence tomography) and deep learning research on the vocal folds. The sexual hormones were discussed, as well as the genetic development of voice production, regulated from the hypothalamus probably related to growth hormone. The primitive integrating voice production centre placed in the motor cortex located over the hand in the homunculus is discussed. Two signal processing brain functions for voice production of voluntary and involuntary processing have different developmental aspects. Updated results of fMRI brain studies are referred to as well as results of tissue examinations.

All these findings are important in the future. Advanced quantitative voice production analysis based on huge amounts of sound information can be combined with artificial intelligence methods to treat voice production deficiencies. In this way developmental disorders of voice production could be diagnosed and treated better.

Keywords: Voice; Development; Childhood; Puberty; Brain; Hormones; Genetics.

Introduction

Adolescence is a challenging time of voice production change, normally and in pathology. The understanding of brain development related to normal voice production development in adolescence and hormonal changes based on genetic stimulation should be updated. Stroboscopy and electroglottography have not achieved quantitative reliable results of voice production usable with Artificial intelligence [1-3]. The technical methods for measuring voice production quantitatively include highspeed films combined with analysis programs, e.g. Glottal Analysis Tools (GAT). Convolution networks analysis of highspeed films with 4000 pictures per second is used in the clinical setting as well as optical coherence tomography (OCT) [4-6]. These methods with high amounts of input information of voice production should be related to other biological measurements, e.g. genetic- hormonal- and brain development.

The aim of the systematic review was to study the relation between measurement of exact voice production development (fundamental frequency and phonetograms), adrenarche and pubertal changes related to hormonal development [7, 8] - to open up for supplementary understanding voice and brain function at the level of genetics. Voice production measurements should be an integrated part in pathology e.g. genetic malformations including cochlear implants [9] as well supplement the very arbitrary definition of pubertal voice break, as it is made in research even now a days by clients 'self-evaluation.

Methods

The systematic search for voice, genetics and cerebral development made by the library of the English Royal Society of Medicine (RSM) at the end only included 9 hand searched papers for the last 10 years, three of them were related to adolescence. Eng-

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Received: November 04, 2020
Accepted: November 10, 2020
Published: November 18, 2020

Citation: Pedersen M, Larsen C. Regulation of Voice Development in Childhood and Puberty, A Review. *Int J Clin Exp Otolaryngol.* 2020;6(6):128-137.
doi: http://dx.doi.org/10.19070/2572-732X-2000024

lish language or foreign language article with an English abstract, human studies and including conference abstracts in Embase were searched (Table 1). (Medline, Embase and hand search 27 March 2020).

The same was also the case for the other search of voice, hormonal, and gender development (Table 2). (Medline, Embase and hand search 9 April 2020). The amount of papers that included voice studies was small, 9, hereof 4 were related to adolescence for the last 10 years. Therefore, we included our own intensive search of other papers often based on reference lists in studies of other subjects - that could be relevant for understanding brain-genetic and pubertal-hormonal development in adolescence also without voice measurements.

The technical evidence-based measurement of various parameters in the complex area of voice has achieved acceptance in recent years [1, 2, 8]. However important objective parameters of normal voice in adolescence may be, they are especially so when pathological deviations must be recognised and defined. It is also possible to a certain extent to describe different qualities of normal voice development in terms of measurable parameters [1].

Regarding Voice analysis, our earlier studies of the child voice

Table 1. The systematic search from the Royal Society of Medicine UK.

Set#	Searched for	Results
S12	s13 or s14	698*
S11	(s1 or s2 or s3) and (s7 or s8 or s9) and (la(english) or abany(yes)) and pd(2010-2020) (la(english) or abany(yes)) and pd(2010-2020)	130
S10	(s1 or s2 or s3) and (s4 or s5 or s6) and (la(english) or abany(yes)) and pd(2010-2020)	595
S9	MJEMB.EXACT.EXPLODE("molecular genetic phenomena and functions") OR MJEMB.EXPLODE("genome") OR MJEMB.EXACT("genetic association") OR MJEMB.EXACT.EXPLODE("genetic association study") OR MJEMB.EXACT.EXPLODE("genetic analysis")	1894215
S8	MJMESH.EXACT.EXPLODE("Genome") OR MJMESH.EXACT.EXPLODE("Genetic Association Studies") OR MJMESH.EXACT.EXPLODE("Genetic Linkage")	460196
S7	ti,ab((gene[*1] or genetic* or genome[*1]) near/3 (voice[*1] or vocal))	176
S6	MJMB.EXACT.EXPLODE("brain") OR MJEMB.EXACT("brain mapping") OR MJEMB.EXACT("brain size") OR MJEMB.EXACT.EXPLODE("brain development")	762303
S5	MJMESH.EXACT.EXPLODE("Brain") OR MJMESH.EXACT.EXPLODE("Brain Mapping")	867287
S4	ti,ab(brain or encephal* or cerebr[*2]) near/5 (chang* or develop* or difference* or structure* or function* or matur* or size*))	569802
S3	MJEMB.EXACT("vocal cord") OR MJEMB.EXACT("voice")	18722
S2	MJMESH.EXACT.EXPLODE("Voice") OR MJEMB.EXACT("Vocal Cords")	14174
S1	ti,ab((voice[*1] or vocal*) near/5 (chang* or develop* or break* or matur*))	13136
* The search starategy retrieved a number of references that were then hand searched to find the most relevant. The details of 9 references have been provided in accordance with your original request.		

The systematic search from the Royal Society of Medicine UK of Voice - genetics and cerebral development March 2020

Table 2. The systematic search from the Royal Society of Medicine UK.

Set#	Searched for	Results
S8	s7 not ti(transgender* or "trans men")	214*
S7	(s1 or s2 or s3) and (s4 or s5 or s6) and (la(english) or abany(yes)) and pd(2010-2020)	222
S6	MJEMB.EXACT("sex hormone") OR MJEMB.EXACT("hormone") OR MJEMB.EXACT.EXPLODE("hormone action") OR MJEMB.EXACT.EXPLODE("sex hormone")	327531
S5	MJMESH.EXACT.EXPLODE("Hormones") OR MJMESH.EXACT.EXPLODE("Sexual Development")	910938
S4	ti,ab((hormone[*1] or hormonal or testosteron* or [*2]strogen* or progesteron*) near/5 (develop* or puberty or chang* or increas* or decreas* or maturation or adolescen*))	264432
S3	MJEMB.EXACT("vocal cord") OR MJEMB.EXACT("voice")	18716
S2	MJMESH.EXACT.EXPLODE("Voice") OR MJMESH.EXACT("Vocal Cords")	14166
S1	ti,ab((voice[*1] or vocal*) near/5 (chang* or develop*))	12589
*The search strategy retrived a number of references that were then hand searched to find the most relevant. The details of 9 references have been provided in accordance with your original request.		

The systematic search from the Royal Society of Medicine UK of Voice -hormonal and gender development April 2020

- boys and girls, was investigated in a stratified study with phonetograms (voice range profiles) and fundamental frequency (F0) in running speech while reading a standard text. The methods were based on development and evaluation of the function of phonetograph 8301 made by the firm Voice Profile. It was combined with electroglottographic and stroboscopic examination of the movements of the vocal folds in speech. 2,000 consecutive stable electroglottographic cycles were measured in 48 boys and 47 girls, aged 8–19 years, to measure fundamental frequency in a standard reading situation. The method for variation in the fundamental frequency by analysis of the electroglottographic histogram configuration was based on the method by Abberton and Fourchin [9]. The voice analysis was compared with measurements of pubertal stages in youngsters and hormonal analysis of all androgens and in girls, also oestrogens.

Regarding Hormonal Status and Pubertal Analysis,the logarithmic criteria that were used, based on geometric cross sections, are considerably stricter than the linear ones. A one-way multivariate analysis was performed, using the fundamental frequency of the speaking voice as classifier to determine whether there were differences between the various groups. For all variables we determined the correlation coefficients, to be able to calculate the relationships between them and their dependency on age by using the partial correlation coefficients. The BMDP (Biomedical Data Pack, UCLA) statistical program was used. In the phonetograms in boys the lower tone descended, and in the girls the tone range during speech widened - the lowering of the SHBG predicted the voice change in boys, and height and oestradiol predicted the log(tone range) in speech. A linear correlation coefficient of SHBG and menarche (1st bleeding period) was found.

Results

Brain, genetics

The brain development of voice related areas in adolescence is mostly genetic. At the beginning the reactivation of the hypothalamic hypophysis gonad axis is a result of a complex network of genes, neurotransmitters, and neuronal interactions in the hypothalamus. It all begins from the nasal placode where from GnRH (gonadotropin releasing hormone) neurons migrated to hypothalamus (Fig. 1) [10, 11].

Brain related voice production research was made by Ludlow [12]. Input and ongoing voice modulation is from the posterior superior temporal gyrus (PSTG) as well as from the supplementary motor area (SMA) and Insula (Fig. 2). Output from the primitive integrative vocalization centre (VOC) was shown by Penfield and Roberts [13]. Black lines in Fig 2 are for the direct pathway via the corticobulbar pathway and the cerebellum (CBL) bilaterally. Grey lines show the pathway from VOC to the cingulate, amygdala nucleus (AM) periaqueductal grey (PAG) the pons and the reticular area in the medulla with input to nucleus ambiguous (NA) on both side of the brain. Human emotionally based vocalisation and volitional voice production have shown more integration than previously proposed- It should be noted that reflexive as well as learned voice production – not involuntary speech – have a common system. Fig.3 is referring to Penfield and Roberts [13] who showed the primitive integrated voice production area in the motor cortex. Planning for brain function of speech production and executional loop for speech have their own discrete pathway, [9, 14] as referred to in Phoniatrics I (2020).Development of voluntary laryngeal control has been argued to be key innervation in the evolution of language. Humans have the described direct cortical innervation of motor neurons controlling the larynx when non-human primates do not. The brain also has cortical circuits for controlling the efferent signals.

McCarthy [15] described in her book, the development of sex and the brain in animals' vs humans. Animal studies are not directly useable in voice studies of humans. This is also the case for Perrodin C. et al., [16], Zaqout S.I and Al-Hussain S.M. [17]. Xie Y. and Dorsky R.I. [18] show the development of brain incl. hypothalamus across vertebrate species. The knowledge of human subcortical development is summarized by Abbott and Burkitt [19]. The division between voluntary and emotional regulation of voice is difficult as discussed by Ludlow [20].

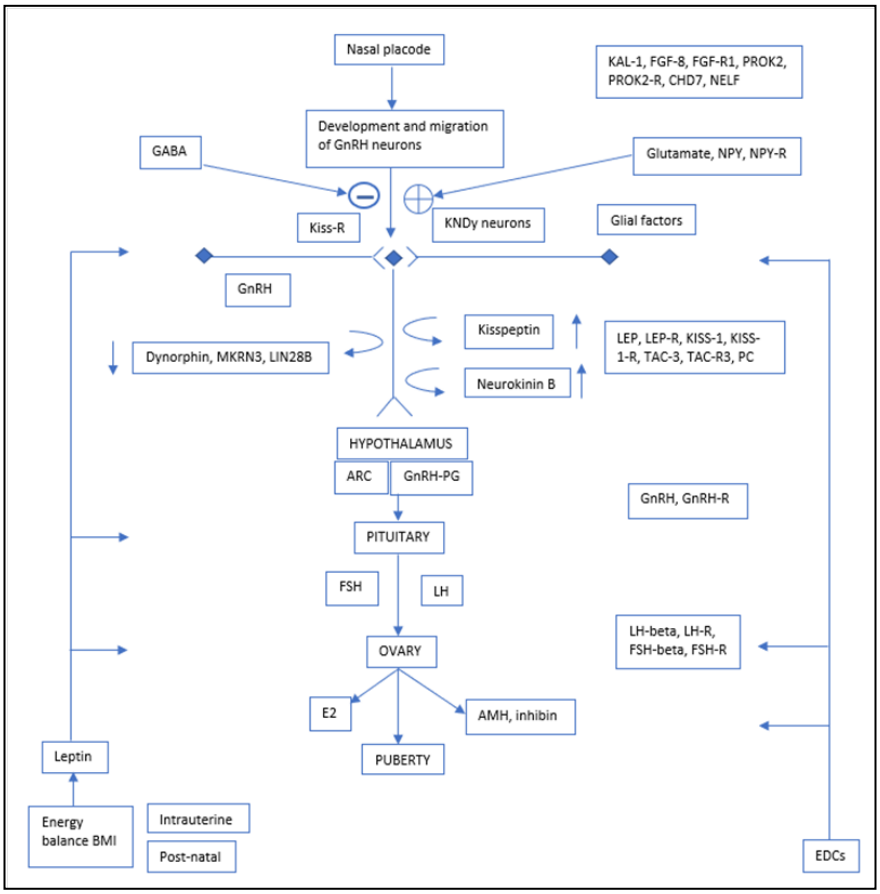
There are basic brain research areas of voice perception, and the vocal consequences of modulation of speech. These are not in our focus, which is also the case for pathology- and singing- in this overview of updating our knowledge of development of the normal voice [21-27]. Other nearby areas of research are related to the fetal and newborn development of voice processing in the brain [28-32]. Rosseli et al., [33] have made a review of language development across lifespan with a neuropsychological/neuroimaging perspective. Many related areas are incorporated in the research to understand development of voice production.

Genetics

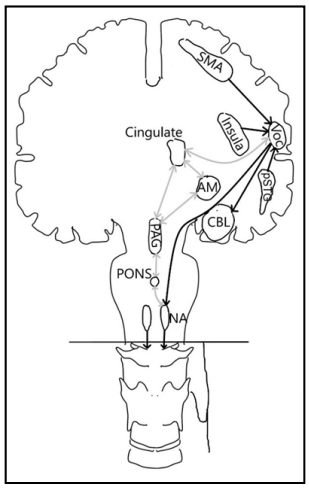
An overview of genetic voice disorders was earlier made [9]. The main reason for this work was that genetic pathology of human development mostly involves voice disorders. The importance of this study was underlined by Sataloff [20]. E.g.voice research in cochlear implants of genetic deafness is seldom randomised [34]. There is a genetic mix of research in the field: Animal studies, new-born studies, pubertal pathology studies, among others. Genetic factors influence vocal quality development but only narratively described in the literature [20].

An overview of the gene FOXP2 has been given [35]. Language-impairment has been found to be associated with FOXP2 encoded regulatory proteins. Day F et al., [36] recognises the biological genetic mechanisms and timing of puberty as important. In the recent large-scale genome wide female developmental study 389 statistically independent signals were found distributed across all 23 chromosome pairs. According to Hollis et al [37], in a male study, 76 independent genetic signals for male puberty was described. The authors found that genetically the voice break in boys was related to menarche in girls. Day et al., [38] also found 2 genes reportedly disrupted in rare disorders of puberty: LEPR and KAL1. Genetic correlations indicated shared aetiologies in both sexes between puberty timing, body mass and other phenomena. Renes et al., [39] describes the dependency of Growth Hormone on normal functions of Growth receptor hormones based on a gene on chromosome 5. Gonadotropin releasing hormone (GnRH) is active in many connections, Forni et al., [40]. The importance of understanding the relation between GnRH and among others fibroblast growth factor was described by Cho [11], the development of GnRH is important for the functional reproductive systems in vertebrates including PAX6, SOX2 and

Figur 1. Presents an overview of the genes involved in puberty regulation with hypothalamus in the centre. The development starts from the nasal placode in the foetus with development and integration of GnRH neurons (gonadotropin releasing hormone expressing neurons).



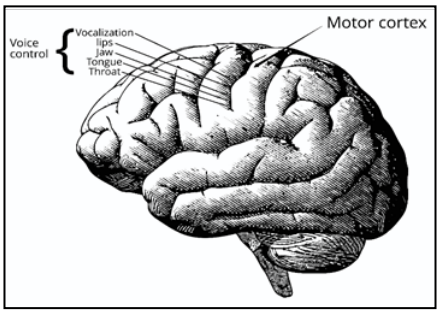
Figur 2. Input and ongoing modulation is from the posterior superior temporal gyrus (pSTG under the VOC) as well as from the supplementary motor area (SMA) and Insula. Output from the primary integrative vocalisation centre (VOC). Black lines are the direct pathway via the corticobulbar pathway and the cerebellum (CBL) bilaterally. Grey lines show the pathway from VOC to the cingulate, nucleus amygdalae (AM), periaqueductal Gray (PAG), the pons and the reticular area in the medulla with input to nucleus ambiguous (NA) on both sides of the brain. From there to the vagus nerve.



FOXG1. Kotler J and Haig [41] focus on anthropology in the difference between vertebrates. A cluster of imprinted genes on human chromosomes 15 and 14, genetic variants in DLK1 are associated with menarche timing in girls and voice break in boys and pathology thereof.

Lardone et al., [42] comment that voice break is a landmark of advanced male puberty in genome wide association studies and have revealed that pubertal timing in a highly polygenetic trait. They refer that although voice breaks are easily recorded in large cohorts, it holds quite low precision as a marker of puberty, 29 significant and independent single nucleotide polymorphisms were extracted associated with age at voice break. In contrast gonadarche and pubarche are earlier and clinically well-defined measures of puberty onset. The genetic and epigenetic approach to puberty is probably important for future aspects as examples in twins for

Figur 3. The primary integrative vocalisation centre in the motor cortex – located over the hand regulator – on both sides of the brain.



specific hormonal disorders e.g. SOX3 [43, 44]. Schriberg et al., [45] have an important updated overview of percentages of neurodevelopmental disorders of speech/motor-speech.

Based on studies in primates, Aboitiz [46] propose a continuous evolution for the auditory vocal apparatus. The articulatory loop also refers to the phonological loop with direct cortical control of the vocal fold musculature and the consolidation of an auditory-articulatory circuit, encompassing auditory areas in the temporoparietal junction and prefrontal and motor areas in the frontal lope. The connection between the anatomical and genetical understanding is still to be developed [46].

Hormones

Based on the review of the literature voice development and hormonal and other pubertal areas could be enlightened. Wierenga et al., [47] show with fMRI that the onset of adolescence give rise to increase in putamen and pallidum volumes and decrease in nucleus accumbens and thalamus volumes with larger volumes in males, and the caudate nucleus, pallidum and hippocampal volumes in females, related to chronological age. Changes in testosterone level were related to development of pallidum, accumbens, hippocampus and amygdala volumes in males and caudate and hippocampal volumes in females. The modeling interaction between pubertal maturation and chronological age seemed to be sex specific.

Etchell et al., [48] admit that sex differences in childhood language development is unclear - in a review of 46 published studies they conclude that sex differences may be more prominent during certain developmental stages due to different rates of maturation between the sexes. They admit that more research is needed to understand the influence of sex hormones and developmental stages. They notice that sex differences in brain structure and function do not necessarily lead to differences in language task performance, and evidence for sex differences in brain and language development are limited, when present, sex differences often interact with a variety of factors such as age and task.

The historic definition of puberty stages 1-5 is referring to Marshall and Tanner [49, 50]. Brook [51, 52] finds in boys "voice break" and "voice change" in stage 3-4 , none in girls - "instead" menarche is given in stage 4.

Styne [53] made a thorough overview of puberty phenomena referring to Tanner, including genetics, hormones etc, voice is not discussed. This is also the case in another survey of puberty by Sultan et al., [10]. The author state that puberty cannot be perceived as a solitary event, they discuss basic genetic changes, and hormonal changes as well as brain changes as earlier referred to in this paper. The concepts are of: 1. adrenarche (of production DHEAS and androstenedione in the adrenals) 2. thelarche, breast development 3. menarche, beginning of menstruation, 4. pubarche, pubic hair development, 5. gonadarche, secondary sex characteristics. Styne [53] also discusses prepubertal values of serum hormone binding globulin (SHBG) and estradioe/ estradiol as general guidelines for prepubertal stage. They point out that the pubertal stages are determined by hormones, and that most of the circulating estradiol and testosterone is associated with SHBG and that prepubertal boys and girls have equal concentration of SHBG.

Henick and Sataloff [20] refer that the mutational voice is between 12,5 and 14 years of age and that the vocal folds in males at 16 years of age are 18-24 mmm long with a fundamental (Fo) of 130 Hertz. In girls, 16 years of age the vocal folds are 15-20mm long and fundamental frequency (Fo) is 220-225. At 6-12 years the vocal folds have two layers, at 16 years the vocal folds have three layers, which is documented with optical coherence tomography [54]. The prevalence of voice problems in the United States are 1.4% +/- 0.1%, [55]. Busch et al., [56] still described "voice break" recurring at 13,6 years (13,5-13,8 years of age). The voice breaks was self-evaluated and corresponded to testis size 11,8 mm (4-20 mm) and genital stage 3 (stage 2-5).

In pathology voice production related to puberty should be much more focused upon, as earlier mentioned e.g. in cochlear implants and in many other developmental disorders e.g. Turner syndrome [57, 58].

Voice production

In adults there seems now to be an acceptance of the functional connectivity of among others, periaqueductal grey (PAG) with core limbic system and laryngeal cortico-motor structures during human phonation, divided in volitional and non-volitional phonation (see Fig. 2 and Fig.3).Galgano et al., [60] states the importance hereof. Holstege&Subramanian [61] underline that only humans can speak because, via the lateral components of the volitional or somatic motor system, they are able to modulate vocalization into words and sentences by activation of the prefrontal area, PAG, and caudal medullary nucleus retro ambiguous (NRA). NRA is the only cell group that has direct access to the motor neurons involved in vocalizations. Guenther [61] suggests that new speech sounds are learned by storing an auditory target of the sound

and then using the auditory feedback control system to control production. Vocal brain control in adults is to some extent agreed upon [62-64]. This research of vocal brain control is also referring to animal studies [65, 66].

With fMRI studies, an interesting understanding of brain development includes analysis of voice processing development, focusing on the temporal-parietal cortex and posterior cingulate/cingulate gyrus decreasing in size during development, while the left posterior and right middle superior temporal regions significantly enlarge [25]. On a large-scale chart for developmental changes in the brain, a focus will be on the pubertal period from 9-17 years of age, and structural plus functional activity will be compared with pubertal hormones and pubertal development [67]. The understanding of the developmental functional synaptic structures is of great interest, Vasung et al., [68] conclude that it remains unclear how among others metabolic demands influence the development.

Acoustics

There was a change of understanding of the human voice with the vowel research made by Peterson and Barney [69]. Much has happened since. Fant [70] in his book of acoustic theory of voice production and Carlson and Fant [71, 72] discussed the isolated vowels. Studies have been made of the role of formants overtone maxima in children [73]. Another important approach is the study of the development of resonances in speech and singing as well. It seems that controlling the acoustic resonances of the vocal tract is an important skill mastered by nearly all children when learning to speak - they learn to move tongue and jaw, lips and soft palate to adjust to vowels and some consonants [74]. Fuchs et al., [75] underline the influence of singing activity on subjects' voice perception and use of voice in childhood and adolescence. Recently Howard et al., [76] are focusing on voice changes in females in puberty as part of a longitudinal study of female choristers. This is since all major cathedrals nowadays have choirs of both boys and girls.

There are many ways of helping youngsters understanding their voices. One is highspeed films where quantitative analysis in typical child populations is of help to illustrate vocal fold movement [77]. Patel [78] analysed children 5-11 years of age with recordings of 30 cycles each and compared them to adults. Children had faster closing phases of the vocal folds, confirming differences found between children and adults by Döllinger et al., [79]. The sex hormone receptors in vocal folds have been focused upon by Nacci et al., [80] but were seldom found. The authors speculate that the changes of voice according to gender throughout life might be linked with a different expression of some growth factor in the laryngeal tissue and that this expression might in turn be influenced by hormonal variation. Interesting is a study from Sato et al., [81] showing that the vocal fold mucosa, unphonetic, without voice, two cerebral palsy children (7 and 12 years old) did not have a vocal ligament, lamina propria appeared as a uniform structure, vocal fold stellate cells synthesized fewer extracellular matrix substances such as fibrous protein and glycosaminoglycan.

Adrenarche

Adrenarche encloses the period just before puberty. Adolescence is the period before the onset of puberty during which a young person develops from a child into an adult. World Health Organisation (WHO) gives 10-19 years for the period. Young people were referred to as being 10-24 years of age. Adrenarche encloses the change of the outer layers of adrenals related to pubic and axillary hair. In a recent large scale genomic study conducted on pubertal development it is clear that genetic timing and age of menarche are relevant, Sultan et al., [10] underlines that the onset of puberty is determined by genetic heritability and neuroendocrine factors (modulated by general health, nutritional adequacy, exercise and environmental chemicals). Styne [53] has an overview. Guran et al., [82] measured the age and DHEA-S secretion in healthy children at adrenarche, where DHEA-S concentration over 108,4 nm/L (40 ug/mL) were regarded as adrenarche at 8 years of age in girls and 7 years for boys. Dörr et al., [83] confirm that DHEA-S were higher in Turner girls without growth hormone therapy, but that the time of adrenarche were the same with or without hormone therapy.

The interests in society in advancing measuring for understanding the voice is referring to hormonal and pubertal changes. Certainly, brain research is part hereof as is the case in many other scientific areas. Whittle et al., [84] focus on adrenarche timing on brain function, in the study of early adrenarche defined by high DHEA-S independent of age of effects on brain function. 83 children, mean age 9,53 (SD 0,34) hereof, 43 female were examined, and a higher DHEA level was associated with decreased affect related activity in the mid-cingulate cortex in the whole sample, and in a number of cortical and sub cortical regions in females. Higher DHEA levels were also associated with increased externalizing psychological symptoms in females that were partly mediated by posterior-insula activation. The author suggests that timing of adrenarche is an important moderator of affect related brain function. Barendse et al., [85] confirm that adrenarche changes in the brain structures are prior to godanarche. In a longitudinal study of DHEA/ DHEA-S and testosterone on fMRI at 9 years, high DHEA suggested negative association with white matter microstructure. Higher values were also related to anxiety symptoms through an effect on amygdala and inferior frontal gyrus. Testosterone was related to the development of white matter. Development of voice production should be much more exact than self-reported voice breakto compare to other parts of body development and pathology [56]. Specific focus on voice development in treated adrenal cortical tumours was made in 9 adults and 10 adolescents female were F0 was reduced to 132 Hertz in 1 and F0 to 165/168 Hz respectively in two subjects. The majority had normal F0, from 189 to 245 Hz [86].

Puberty

There are some aspects of early development that influence the voice related hormonal situation in pubertal youngsters: Especially the "mini-puberty" around birth and growth hormones. A problem is that a lot of research on hormones is on primates/non-humans, which means that even if some results are common – when it comes to human voice, they can probably not be used. For the "mini-puberty" around perinatal life it is important to understand that peripheral hormones in blood serum are regulators in a transitory hormone surge that is comparable in its extent to puberty [87, 88]. In the same group, Quast et al., [89] even found a robust positive relationship between four week concentration of estradiol and individual articulatory skills, in contrast testosterone concentrations at 5 months negatively correlated with articulatory

skills at the same age in both boys and girls. Borysiak et al., [90] noted that F0 properties were correlated to average serum levels of bio available estradiol (E2) (mean E2/SHBG and testosterone/mean testosterone across the second month of life. They interpreted the results as indication of E2 influence on viscoelastic properties of vocal folds.

Aguiar-Oliveira et al., [91] present a study on humans with IGHG gene-type 18 owing to a mutation of Growth hormone receptor hormone gene (GnRHr) with severe reduction of growth hormone which also resulted in voices that were high-pitched. Valenca [92] and their group also found in untreated isolated growth deficiencies that most voices had higher formant frequencies than normal, with a prepubertal acoustical structure. De Andrade [93] and their group showed that voice problems in patients with growth hormone deficiency could be improved with the voice therapy of semi occluded vocal tract voice training.

When it comes to human voice, non-human studies still can be necessary. In rats [94, 95] a study was made on the role of voice change on the vocal folds, especially the extracellular matrix (ECM) in vocal fold lamina propria. The hyaluronic acid decreased in ovariectomized rats. The collagen-1 was lowered, this was also the case of collagen-3 later in the observational period. Elastin was less dense in the same rats. They suggest that the vocal folds are an estrogen sensitive target organ.

The sexual forms of nuclei in arcuate- and antero-ventral- periventricular nuclei account for the differential behavior of the hypothalamic-pituitary-gonadal axis between genders [96]. Shirtcliff and her group [97] suggest that there is a "coupling" between the hypothalamic-pituitary-gonadal axis and the gonadal axis. The limbic and related circuits are activated as the first stage of stress with a secondary hypothalamic activation. These results are of interest also in young singers. The study of Hodges-Siemon [98] and her group on testosterone and vocal parameters in 91 adolescent male indicated that males in better energetic conditions (BMI-for-age residuals from Tanner-specific growth curves) have higher testosterone and lowered voice even controlling for age.

The knowledge of sex related hormones is as important as ever. Testosterone given to females is a well-known risqué of voice lowering [99]. Voice changes should be considered whenever hormonal treatment is used. Wuntakal et al., [100] refer to some effects of LHRH agonists given for ovarian cancer. Zacharin [101] has an overview of treatment of secondary hypogonadism of treated severe illness in childhood and adolescents since many children now survive chronic illnesses.

Prediction of voice change in puberty

Table 3 and 4 show results of voice production development in prepubertal, pubertal and post pubertal groups in boys and girls [7, 8].

Shirtcliff [102] has made an overview of hormonal change in puberty where it was shown that a picture-based interview combined with testosterone, DHEA and physical exam gave better predictive values. SHBG had a predictive significance of voice change in boys of $p<0.05$, in girls the widening of the range of the fundamental frequency in semitones during speech and E1So4 measureshad predictive values of $p<0,05$ [7].

Gaidano et al., [103] found that mean values of SHBG binding capacity, both for dihydrotestosterone and testosterone were significantly higher in prepubertal subjects. The binding capacity of SHBG is a result of a pool of proteins which modifies pubertal evolution.Rosner et al., [104] discus SHBG as a cell regulator, they demonstrate an additional mode of action on steroid hormones, one that does not require that the steroid interacts with a receptor. Kim et al., [105] measured SHBG which decreases markedly during early puberty. They found that 50 nm/L in stage Tanner 2 were significantly different to Tanner stage 1 and that free androgen index (FAI = testosterone/SHBG) could even better differentiate the onset of puberty. The decrease of SHBG coincidence with a significant increase in total body weight and body mass index. Simo et al., [106] describe how sex hormone binding globulin (SHBG) is produced and secreted by the liver into the bloodstream where it binds sex steroids and regulates their bio-

Table 3. Geometrical average of hormonal, pubertal and vocal parameters for boys.

Age	(years)	8.7-12.9	13.0-15.9	16.0-19.5 pr yr.	% change
No of boys		19	15	14	
Serum testosterone	(n mol/l)	0,54	10,5	18,9	68
Dihydrotestosterone	(n mol/l)	0,18	1,21	1,57	37
Free testosterone	(n mol/l)	0,007	0,14	0,33	77
Sexual hormone binding globulin	(n mol/l)	134	66	45	-16
Delta 4 androstenedione	(n mol/l)	0,54	1,17	2,5	24
Dehydroepiandrosteronesulfate	(n mol/l)	1400	4100	5900	25
Testis volume	(ml)	2,3	13	20	36
Fundamental frequency	(Hz)	237	184	125	-11
Voice range	(semitones)	3,7	4,8	5	3,9
Phonetogram area	(cm2)	19	28	34	9,2
Lowest biological tone	(Hz)	158	104	72	-12

Geometrical average of hormonal, pubertal and vocal parameters for boys grouped according to pre-pubertal, pubertal, post-pubertal age and the annual change in these parameters in %. (Phonetogram area: 1 cm2 = 32 semitones x dB(A)),(Redrawn from [7, 8])

Table 4. Geometrical averages of hormonal, pubertal and vocal parameters for girls.

Age	(years)	8.7-12.9	13.0-15.9	16.0-19.8	Significance
Total number		18	12	11	
Oesterone (E1)	pmol	57	104	123	**
Oestradiol (E2)	pmol	73	135	108	
Total testosterone	nmol	0,5	0,76	0,94	
Free testosterone	nmol	0,006	0,037	0,009	
Oesterone sulphate (E1SO4)	pmol	732	1924	2342	**
DHEAS	nmol	3210	3700	7200	**
Androstendione	nmol	1,44	3,28	3,43	*
Sex hormone binding globulin (SHBG)	nmol	153	130	123	
Menarche		4	9	11	
Pubic hair stage		4-Jan	5-Feb	6-Apr	
Mamma development stage		4-Jan	5-Feb	5	
Fundamental frequency in continuous speech	Hz	256	248	241	
Tone range in continuous speech	Semitones	3,7	4,2	5,2	**
Tone range in singing	Semitones	23	30	38	
Phonetographic area	cm2	17,3	21,8	28,3	**
Phonetogram lowest tone	Hz	166	156	145	*
Phonetogram middle tone	Hz	429	409	413	
Phonetogram highest tone	Hz	1136	1105	1263	

Geometrical averages of hormonal, pubertal and vocal parameters for girls grouped according to pre-pubertal, pubertal, post-pubertal age. The relative standard deviation lay between 11% and 140%. (Significance of the differences between the groups: $p < 0.01$ xx; $p < 0.05$ x). Cm2 conversion factor: 1 cm^2 = 32 semitones x dB(a), (Redrawn from [7, 8]).

availability, by limiting their diffusion into their target tissue.Further research is needed to elucidate the molecular mechanism that could explain the sexual dimorphism regarding the plasma SHBG levels. Laurent et al., [107] comment that the in-vivo physiological role of circulating SHGB remains unclear, transgene mice expressing a human SHBG transgene were used in their study. The results are not directly translated for human voice related connection. SHGB is an interesting factor in prediction of voice change in puberty in Tanner stage 2-4 due to its' multifactorial tissue effects.

Discussion and Conclusion

A systematic search was made of the last 10 years of development of voice production in adolescence. 18 papers were found in a search of Medline, Embase and hand search by the library of the English Royal Medical Society. Many indirect relevant studies of voice production development were found in reference lists. It was shown how voice production development is connected to genetic and brain development. This is of main value for understanding pathology. The genetic development of voice production is regulated from the hypothalamus probably related to growth hormone. The brain development is related to the primary voice production, confirmed with fMRI, synchronized from the primary integrated vocalmotor cortex center - over the hand - in the homunculus. Hormonal development and especially the Serum Hormone Binding Globulin have a predicting role for the development of voice production in puberty which is not fully understood [108]. Stroboscopy and electroglottography are used routinely for voice diagnostics without quantitative parameters [2, 3, 7]. In the future combined updated online highspeed film measures of voice production can give a much better quantitative understanding of voice production development [4, 5] - eventually combined with optical coherence tomography [6] and analyzed with neural networks [1]. Especially in pathology, mostly genetic multihandicaps´ syndrome patients could get better treatment if quantitative measures of several kinds of examinations were used [9].

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