The spinal control of ejaculation revisited: a systematic review and meta-analysis of anejaculation in spinal cord injured patients

Clément Chéhensse¹, Stéphane Bahrami²,3, Pierre Denys¹,4, Pierre Clément¹, Jacques Bernabé¹, and François Giuliano¹,4,*

¹EA 4501 SIRIUS, Université de Versailles Saint Quentin en Yvelines, Montigny-Le-Bretonneux, France ²EA 4497 GRCTH, Université de Versailles Saint Quentin en Yvelines, Montigny-Le-Bretonneux, France ³Public Health Department, Raymond Poincaré Hospital, APHP, Garches, France ⁴Neuro-Uro-Andrology, Department of Physical Medicine and Rehabilitation, Raymond Poincaré Hospital, APHP, 104 bd Raymond Poincaré, 92380 Garches, France

*Correspondence address. Tel: +33147107748; Fax: +33147104443; E-mail: francois.giuliano@uvsq.fr

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BACKGROUND: After spinal cord injury (SCI), most men cannot ejaculate without medical assistance. A major advance in the knowledge of the spinal control of ejaculation has been achieved with the discovery of a spinal generator of ejaculation (SGE) in the rat. The aim of this report was to review studies about ejaculation after SCI in order to revisit the spinal control of ejaculation and especially to assess the existence of an SGE in man.
Introduction

The incidence of traumatic spinal cord injury (SCI) is estimated at 16/million/year in Western Europe and 39/million/year in North America with a prevalence of 300/million and 853/million, respectively (Cripps et al., 2011). Nowadays, the life expectancy of SCI patients tends to be close to that of the general population (Middleton et al., 2012). In the USA, the mean age at occurrence of SCI is 37.1 years and 77.1% of SCI patients are male (Devivo, 2012). In addition to motor and sensory loss, uro-genito-sexual functions are severely impaired by SCI including, in males, erection and ejaculation, causing major sexual and fertility issues. Among the patients’ priorities regarding recovery, sexual function is the highest in paraplegic patients and the second highest in quadriplegic patients (Anderson, 2004). Many SCI males have not fulfilled their parental project at the time of the trauma. Fatherhood is still possible although it often requires specialized medical management which can be complex, time-consuming, expensive and not totally devoid of safety issues for the patients as well as their female partners.

Ejaculation can be physiologically defined as the rhythmic forceful expulsion of semen at the urethral meatus. Ejaculation comprises two successive phases, emission and expulsion, each involving different pelvic perineal anatomical structures (Giuliano and Clement, 2005). Emission is controlled by autonomic (sympathetic and parasympathetic) spinal centres and expulsion is controlled by somatic spinal centres. These centres act in synchrony in order for antegrade ejaculation to occur. Such a synchronization has been reported to be led, in rats, by a group of lumbar spinthalamic neurons forming a spinal generator of ejaculation (SGE). The critical role of the SGE and its organization have been described during the last decade in functional and neuroanatomical studies (Truitt and Coolen, 2002; Xu et al., 2005, 2006; Borgdorff et al., 2008; Sun et al., 2009). In rats, the SGE is located in lamina X and the medial part of lamina VII, around the central canal, at the third and fourth lumbar (L3–L4) spinal segments (Fig. 1).

The SGE activity is influenced by peripheral and brain inputs which can either be excitatory or inhibitory. Neurons belonging to the brain circuitry specifically controlling ejaculation have been identified in rodents (Coolen et al., 1998; Heeb and Yahr, 2001; Hamson and Watson, 2004), although their exact role and nature are not yet fully delineated. Overall, a major advance in the understanding of the experimental neurophysiology of ejaculation has been achieved.

In humans, the innervation of anatomical structures involved in ejaculation is organized in a similar manner to that in rats. Due to differences in metamerization between the two species, there are slight differences in the spinal cord segments in which preganglionic autonomic neurons and somatic motoneurons are located. In the human spinal cord (Fig. 2), the parasympathetic centres located in the intermediolateral cell column (IML) of the S2–S4 segments innervate the accessory sex glands, i.e. the seminal vesicles and the prostate (Onufrowicz, 1899). The sympathetic centres located in the IML and the dorsal grey commissure of the lower thoracic and upper lumbar segments innervate the smooth muscle cells of the entire seminal tract, including the epididymis, the vas deferens, the seminal vesicles, the prostate, the prostatic urethra and the bladder neck. For the sympathetic centres which control the ejaculation, depending on the authors, the upper limit is T9, T10 or more often T11 and the lower limit is L2 or L3. According to earlier anatomical studies of sympathetic innervation, the cell bodies of preganglionic sympathetic neurons innervating the accessory glands are mainly located in segments L1 and L2 (Müller and Dahl, 1912) with their axons reaching the paravertebral sympathetic ganglia and the hypogastric plexus (Dejerine, 1914). Furthermore, after sympathectomy, ejaculation is the most impaired after bilateral removal of the TI2 – L2 paravertebral sympathetic ganglia (Whitelaw and Smithwick, 1951; Courty and...
Accordingly, the most likely location for the sympathetic ejaculation centres in humans is between T12 and L2. Onuf’s nucleus, which contains the cell bodies of the motoneurons and innervates the pelviperineal striated muscles including the bulbospongiosus and ischiocavernosus muscles, is located in the ventral horn of the S2–S4 segments (Onufrowicz, 1899; Dejerine, 1914; Chapelle et al., 1985; Schroder, 1985).

SCI impairs motor, sensory and autonomic functions. Three classifications have been successively proposed to characterize the SCI: Frankel’s classification (Frankel et al., 1969), the University of Miami Neurospinal Index (UMNI; Klose et al., 1980) and the American Spinal Injury Association Impairment Scale (AIS; Kirshblum et al., 2011) which is the most widely used. Each classification provides two different kinds of information: (i) the most cranial injured segment for Frankel’s classification and...
the most caudal intact segment for the UMN and AIS classifications (Fig. 3) and (ii) the degree of impairment of motor and sensory functions below the lesion ranked using letters from A to E with A = complete motor and sensory injury, B = complete motor but incomplete sensory injury, C/D = incomplete motor and sensory injury and E = normal motor and sensory functions.

The innervation of somatic motor effectors is under the control of the cortico-spinal tract and is constituted of two successive motor neurons. The upper motor neurons (UMN) originate in motor regions of the frontal cortex. Their axons are located in the white matter of the spinal cord. The UMN synapse with lower motor neurons (LMN) in the anterior horn of each spinal segment. Above the level of the lesion, the spinal cord is intact with normal motor and sensory function. At the level of the lesion, the grey matter is damaged (LMN lesion) and voluntary and reflex striated muscle contractions are abolished. In addition, the white matter in which UMN axons travel is also damaged (UMN lesion). Thus, below the level of the lesion, LMN remain uninjured but are disconnected from UMN and pathways of supraspinal origin. Voluntary muscle contractions are abolished but reflex muscle contractions can still occur, especially in response to noiceptive stimuli (Giovanelli Barilari and Kuypers, 1969; Kostyuk et al., 1971; Faganel and Dimitrijevic, 1982).

The three SCI classifications mentioned above have limitations in that they only specify the upper limit of the lesion and its degree of completeness. However, neither the lower limit of the lesion nor the functional status of spinal segments below the lesion are documented. For instance, in the case of an SCI patient classified T7 AIS A, equivalent to T7 UMNI A or T8 Frankel A, the lesion could actually extend from T8 to

(i) T2, thus causing direct lesions of the sympathetic ejaculation centres, but the parasympathetic and somatic ejaculation centres would be infralesional (Fig. 2a) or

(ii) L2, thus causing direct lesions of the sympathetic ejaculation centres, but the parasympathetic and somatic ejaculation centres would be infralesional (Fig. 2b) or

(iii) S5 causing lesions of the autonomic and somatic ejaculation centres (Fig. 2c).

The lower limit of the lesion can be estimated based on the testing of spinal reflex arcs relative to motor metamerization (Grossiord et al., 1963; Chapelle et al., 1983b; Previnaire et al., 2009; Fig. 4). Accordingly, careful physical examination provides crucial information regarding the extent of the SCI.

Even though normal ejaculation, i.e. rhythmic forceful ejaculation is often abolished, ejaculation can still occur in response to peripheral stimulation in complete SCI patients (Brackett, 1999; Fode et al., 2012). This means that normal ejaculation can be elicited when there is a complete disruption of the connections between the brain and the spinal centres which control ejaculation. In other words, coordination between the autonomic and somatic spinal centres which control emission and expulsion can still occur without any supraspinal input. This leads to the hypothesis that an SGE might also exist in humans. In rats, the lower limit of sympathetic ejaculation centres is in the L2 segment, as in humans, and the SGE is located within the L3 and L4 segments. The upper limit of parasympathetic and somatic ejaculation centres is in the L6 segment in rats. The L6 segment in rats corresponds to S1 in humans due to a difference in metamericization between species (Fig. 1). The upper limit for the parasympathetic and somatic ejaculation centres is more caudal in humans, i.e. S2. By considering interspecies differences, we hypothesize that a putative SGE in man should be located between the L3 and L5 segments.

After SCI, most men cannot achieve ejaculation during masturbation or coitus. In a significant number of these patients, the application of supraphysiological peripheral stimulation by penile vibratory stimulation (PVS) on the glans penis can elicit ejaculation. PVS thus represents the first-line method for sperm retrieval in SCI patients with anejaculation. In the case of failure, spermatozoa are sometimes collected by electroejaculation (EEJ) using a rectal probe or are surgically retrieved from the epididymis or the testis (Brackett et al., 2010b). Penile stimulation during masturbation, coitus or PVS recruits a reflex arc at the spinal cord level and therefore involves the spinal ejaculation centres. In contrast, during EEJ, the electric current directly stimulates peripheral nerves in the vicinity of the anterior rectal wall as well as the seminal vesicles and smooth muscle fibres of the prostate. Even though a similar pattern of activation of the smooth and striated urethral sphincters has been reported, the SGE in man should be located between the L3 and L5 segments.

In the case of failure, spermatozoa are sometimes collected by electroejaculation (EEJ) using a rectal probe or are surgically retrieved from the epididymis or the testis (Brackett et al., 2010b). Penile stimulation during masturbation, coitus or PVS recruits a reflex arc at the spinal cord level and therefore involves the spinal ejaculation centres. In contrast, during EEJ, the electric current directly stimulates peripheral nerves in the vicinity of the anterior rectal wall as well as the seminal vesicles and smooth muscle fibres of the prostate. Even though a similar pattern of activation of the smooth and striated urethral sphincters has been reported during PVS and EEJ-induced ejaculation (Sonksen et al., 2001), ejaculation during EEJ does not solely rely on the recruitment of intraspinal pathways. On demand pharmacological treatment can improve the occurrence of ejaculation in SCI patients with anejaculation. Guttmann (1949) first reported the use of the acetylcholinesterase (ACHE) inhibitor prostigmine delivered intrathecally (i.t.) to elicit ejaculation in SCI men. The use of prostigmine was then stopped because of potential lethal adverse effects, i.e. severe autonomic dysreflexia (AD). Subcutaneous (s.c.) delivery of another ACHe inhibitor, phystostigmine, was then used in SCI patients to facilitate ejaculation induced by hypotension (Chatelle, 1979). The use of this compound was then also stopped because of potential severe AD. Midodrine, an a1-adrenergic receptor agonist registered for the treatment of orthostatic hypotension (Lossnitzer and Letzel, 1983; Wright et al., 1998), increases the rate of
ejaculation in SCI patients when combined with PVS (Soler et al., 2008). Accordingly, on demand midodrine prior to PVS should be tested in the case of anejaculation due to SCI when PVS alone has failed.

The aim of this systematic review was to study male ejaculation capacity following SCI in the light of recent progress in the knowledge of the physiology of ejaculation, and to focus on spinal cord circuitry. We particularly wished to gather data supporting the existence of an SGE in human. In order to achieve this, we examined ejaculation occurrence as a function of different features of SCI, i.e. whether spinal ejaculation centres were (i) supra lesional (located above the level of the injury) therefore intact (ii) injured (UMN lesion) or (iii) infra lesional (located below the level of the injury: LMN lesion; Fig. 2). In other words, we aimed to investigate how much ejaculation is impaired in the case of lesions of the sympathetic (T12–L2) and/or parasympathetic and somatic ejaculation centres (S2–S4) and/or the L3–L5 segments in which the putative SGE is located.

**Methods**

**Eligibility criteria**

All original articles published in peer-reviewed journals specifying, in SCI adult men, the occurrence of antegrade rhythmic forceful or dribbling ejaculation (primary criterion) as a function of the neurological characterization of the lesion (secondary criterion) were retrieved.

**Search strategy**

Bibliographic searches were conducted using the following databases: MEDLINE (October 1964 to November 2012), EMBASE (October 1964 to November 2012), EBSCOhost (August 1955 to November 2012) and the Cochrane Library (September 1967 to November 2012). Searches were carried out using the following terms: ("Ejaculation"[Mesh]) OR ("Fertility"[Mesh]) AND ("Spinal Cord Injuries"[Mesh]) OR ("Paraplegia"[Mesh]) OR ("Quadriplegia"[Mesh])).

**Selection criteria**

In order for a study to be included in the systematic review, the article had to provide minimal details regarding the SCI, either the upper limit of the lesion or data regarding the evaluation of somatic spinal reflex arcs (Fig. 4). The exclusion criteria were as follows:

(i) Evaluation of ejaculation elicited by EEJ.

(ii) Inability for the reader to discriminate between ejaculation and climax because of not enough data being provided.

**Data extraction**

The following data were noted for each patient group or individual when available:

(i) Study design and characteristics

(ii) Patient characteristics: age, duration of SCI

(iii) Sexual function prior to SCI

(iv) Completeness of the lesion

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**Figure 4** Sacral, lumbar and thoracic testing of spinal reflex arcs relative to motor metamerization to determine the lower limit of the injury (green, sensory afferents; red, motor efferents) in the case of complete SCI. Pinching or pricking upper, intermediate or lower abdominal skin elicits abdominal muscles contraction (segments T7–T8, T9–T10 and T11–T12). Scratching the skin of the upper thigh (dermatome L1) elicits cremasteric muscle contraction and elevation of the testis (segment L1). Nociceptive stimulation of the sole of the foot (dermatome and segment S1) elicits RHF (segment L2). Pricking or pinching penile glans (dermatome S3) elicits ischio cavernous muscle (segment S3) and external anal sphincter (segment S4) contraction.
between the L3 and L5 segments, we controlled for the lesional status of the L3–L5 segments. The reference rates were then compared between lesion and control groups using statistical methods such as a stratified bivariate analysis, which was used to assess the effect of concurrent lesions of different spinal segments. We also performed a meta-analysis to estimate the reference ejaculation rates for each procedure used to elicit ejaculation.

Data synthesis

Studies were initially grouped according to the procedure used to elicit ejaculation and mean ejaculation rates were calculated accordingly. For PVS, ejaculation rates were compared between studies using optimal settings, i.e., an amplitude of 2.5 mm and a frequency of 100 Hz (Sonksen et al., 1994) and studies using other settings. An impact of the duration of SCI on the ejaculation rate has already been assessed.

Self-reported data from the patient about ejaculation are less accurate than ejaculation elicited in laboratory conditions in the presence of an investigator. Indeed, patients are prone to confuse semen with urine leaks or secretions from bulbo-urethral glands which precede ejaculation. Therefore, in order to provide reliable data, we also reduced the selection of articles in which ejaculation was elicited in laboratory conditions, documented by an investigator, when studying ejaculation rates as a function of the lesion status of the spinal segments.

Reference ejaculation rates were first calculated in patients (i) with complete lesions of the T12–5S segments and (ii) with lesions strictly localized above T12. The reference rates were then compared between lesion levels: T12–L2, L3–L5 and S2–S4 in order to confirm the importance of the T12–L2 and S2–S4 segments in ejaculation and to explore the role of the L3–L5 segments.

Finally, in order to specifically investigate the hypothesis of an SGE located between the L3 and L5 segments, we controlled for the lesion status of known spinal ejaculation centres to determine whether lesions of these segments lowered the ejaculation rate.

Statistical analysis

Ejaculation rates were reported with their corresponding binomial 95% confidence interval and compared using a χ² test or Fisher’s exact test when appropriate. Meta-analyses were performed to estimate the reference ejaculation rates for each procedure used to elicit ejaculation. Pooled estimates were calculated using random effect models in view of the heterogeneity between the observational studies included in the present review; estimates in subgroups, where the completeness or extent of the injury were controlled, were calculated under the fixed-effect assumption (using sample size weights). The impact of the duration of SCI on ejaculation was assessed using (i) an inverse variance weighted linear regression for grouped data and (ii) a logistic regression for individual data. The simultaneous effect of concurrent lesions of different spinal segments was assessed by means of a stratified bivariate analysis. Statistical tests were performed at the 0.05 significance level. All statistical analyses were performed using the Stata 12.0 software (College Station, TX, USA).

Results

Identification

The search strategy yielded 513 publications but 474 were excluded (Fig. 5). Thus 39 articles were identified from the databases and 10 additional studies were identified following cross-checking of references in the selected articles. There were three articles further excluded because cohorts of included patients were the same as in another publication (Comarr, 1971; Sonksen et al., 1994; Courtois et al., 2011) and one was excluded because the cohort was enlarged in a later publication (Brackett et al., 2007b). Therefore 45 articles were finally included.

Qualitative synthesis of studies included

Data from the 45 selected articles are summarized in Tables I–III. Data for ejaculation in 3851 SCI patients were pooled together. Patient characteristics and data retrieved from each study were very heterogeneous. There were 40 articles were about sexual function or fertility in SCI patients (Horne et al., 1948; Munro et al., 1948; Zeiltin et al., 1957; Bors and Comarr, 1960; Money, 1960; Comarr, 1970; Guttmann and Walsh, 1971; Jackson, 1972; Pera, 1973; Fitzpatrick, 1974; David et al., 1977; Comarr and Vigue, 1978; Grossiord et al., 1978; Francois et al., 1980; Brindle, 1981; Chapelle et al., 1982; 1983a, Francois et al., 1983; Sjogren and Egberg, 1983; Brindle, 1984; Sarkarati et al., 1987; Chapelle et al., 1988; Beretta et al., 1989; Slot et al., 1989; Sazsz and Carpenter, 1989; Oates, 1990; Rawicki and Hill, 1991; Alexander et al., 1993; Egon et al., 1994; Nehra et al., 1996; Ohi et al., 1996; Denys et al., 1998; Bird et al., 2001; Sonksen, 2003; Hamid et al., 2006; Soler et al., 2007; Tas et al., 2007; Courtois et al., 2008; Brackett et al., 2010a; Soler et al., 2011). A further three articles dealt with hormonal or testicular function (Morley et al., 1979; Chapelle et al., 1993; Oudem et al., 1995), one article was about emotional feelings (Hohmann, 1966) and another one article was about the function of the infralesional spinal cord segments (Kuhn, 1950). These 45 articles were included in the quantitative synthesis (Moher et al., 2009). Sample sizes ranged from 5 to 529 patients with a median of 44 patients. All but nine studies were retrospective and five studies were multi-centre (with up to three centres). As there was no cohort study, the longitudinal evaluation of the ejaculate rate over time for a similar group of patients was not available. Sexual function prior to SCI was specified in four studies (n = 98; Money, 1960; Hohmann, 1966; Sjogren and Egberg, 1983; Alexander et al., 1993) and each time characterized as normal.

Another source of heterogeneity came from the methods used for sperm retrieval since practices have changed between 1948 and 2012. The ejaculation rate during masturbation or coitus without the aid of medications or devices was specified in 28 studies (Table I), elicited by PVS in 21 studies (Table II) and after masturbation following i.t. prostigmine (0.25 to 1.5 mg), in 2 studies or s.c. physostigmine (1–2 mg) in 5 studies (Table III). Settings of the device used to perform PVS were in accordance with optimal settings (amplitude 2.5 mm, frequency 100 Hz; Sonksen et al., 1994) in 10 studies. Patients were treated with midodrine (5–30 mg) prior to PVS in two studies.

Reliability of data about the occurrence of ejaculation and characterization of ejaculation as rhythmic forceful or dribbling depended on the method used to obtain ejaculation. Ejaculation during masturbation or coitus without the aid of medications or devices occurred in laboratory conditions documented by an investigator in five studies and was self-reported by the patients in 23 studies. Ejaculation elicited by PVS or masturbation following i.t. prostigmine or s.c. physostigmine always occurred in laboratory conditions. There were 42 studies which specified the upper limit of the SCI. Regarding SCI classification, the AIS was used in 12 studies, the UMIN in 2 studies, the Frankel’s classification in 21 studies and in 1 study the classification was not specified. Individual patient data were provided in 13 studies. In 30 studies, data were calculated from subgroups of patients as a function of the upper limit of the SCI. The methods used to group patients differed between studies,
thus little data could be used to assess the ejaculation rate as a function of the location of the lesion. Spinal reflex arcs were tested in 18 studies. The spinal segments tested were T6, T10 or T12 to S5 in 3 studies, S2–S4 in 11 studies, S1–L2 in 4 studies, L1 in 1 study and T12–L2 in 1 study. Only 4 studies specified the evaluation of the spinal reflex arcs of each segment. Ejaculation was specified as rhythmic forceful or dribbling in nine studies.

**Overall ejaculation rates according to the type of stimulation**

Ejaculation rates were obtained from all patients, i.e. with a complete or incomplete lesion, whatever the location of the lesion.

There were 28 articles which provided data about ejaculation during masturbation or coitus without the aid of medications or devices (Table I). Ejaculation was elicited in laboratory conditions in five of these studies (Horne et al., 1948; Francois et al., 1983; Alexander et al., 1993; Courtois et al., 2008; Brackett et al., 2010a; Fig. 6). During masturbation or coitus, the overall ejaculation rate was 16.0% (CI 2.5–19.5). It was 11.8% (n = 1,661, CI 10.1–13.8) in patients with complete SCI (Horne et al., 1948; Munro et al., 1948; Kuhn, 1950; Bors and Comarr, 1960; Money, 1960; Hohmann, 1966; Comarr, 1970; David et al., 1977; Comarr and Vigue, 1978; Grossiord et al., 1978; Brindley, 1981; Chapelle et al., 1982; Francois et al., 1983; Siogren and Egberg, 1983; Slot et al., 1989; Alexander et al., 1993; Denys et al., 1998) and 33.2% (n = 343, CI 28.5–38.4) in patients with incomplete SCI (P < 0.001; Horne et al., 1948; Munro et al., 1948; Bors and Comarr, 1960; Comarr, 1970; David et al., 1977; Comarr and Vigue, 1978; Brindley, 1981; Francois et al., 1983; Slot et al., 1989; Alexander et al., 1993; Denys et al., 1998). For the remaining 1,005 patients, the ejaculation rate according to the completeness of the injury was not specified (Zeitlin et al., 1957; Jackson, 1972; Fitzpatrick, 1974; Morley et al., 1979; Francois et al., 1980; Brindley, 1984; Beretta et al., 1989; Rawicki and Hill, 1991; Tas et al., 2007; Courtois et al., 2008; Brackett et al., 2010a).

There were 21 articles which provided data about ejaculation elicited by PVS (Table II). PVS has always been used as a first-line treatment after the failure of masturbation or coitus without the aid of medications or devices. The overall ejaculation rate with PVS was 52.1% (CI 45.3–58.9; Fig. 7). It was 47.4% (n = 597, CI 43.4–51.4) in patients with complete SCI (Piera, 1973; Francois et al., 1980; Brindley, 1981; Francois et al., 1983; Brindley, 1984; Beretta et al., 1989; Szasz and Carpenter, 1989; Egon et al., 1994; Odum et al., 1995; Ohl et al., 1996; Hamid et al., 2006; Soler et al., 2007) and 52.8% (n = 305, CI 47.2–58.3) in patients with incomplete SCI (P = 0.14; Piera, 1973; Francois et al., 1980; Brindley, 1981; Francois et al., 1983; Brindley, 1984; Beretta et al., 1989; Szasz and Carpenter, 1989; Egon et al., 1994; Odum et al., 1995; Ohl et al., 1996; Hamid et al., 2006; Soler et al., 2007). For the remaining 1,009 patients, the ejaculation rate according to the completeness of the injury was not specified (Sarkarati et al., 1998; Oates, 1990; Rawicki and Hill, 1991; Nehra et al., 1996; Bird et al., 2001; Sonksen, 2003; Soler et al., 2007; Courtois et al., 2008; Brackett et al., 2010a).

There were seven articles which provided data about ejaculation in response to masturbation following i.t. prostigmine or s.c. physostigmine (Table III). In five studies, i.t. prostigmine or s.c. physostigmine was used after failure of masturbation or coitus without the aid of medications or devices, with an overall ejaculation rate of 57.1% (CI 51.6–62.5; Fig. 8a). This rate was 54.7% (n = 309, CI 49.1–60.2) in patients with complete SCI (Guttmann and Walsh, 1971; Grossiord et al., 1978; Chapelle et al., 1983a, 1988, 1993) and 78.1% (n = 32, CI 61.8–89.3) in patients with incomplete SCI (P = 0.014; Guttmann and Walsh, 1971). In two studies, physostigmine was used after PVS failure with an ejaculation rate of 37.6% (CI 7.4–67.8; Fig. 8b). This rate was 17.9% (n = 56, CI 9.8–30) in patients with complete SCI (Piera, 1973) and...
## Table I Ejaculation elicited by masturbation or coitus, without the aid of medications or devices.

<table>
<thead>
<tr>
<th>First author/country</th>
<th>Age: mean/ range (years)</th>
<th>SCI classification/ individual data</th>
<th>Testing of spinal reflex arcs</th>
<th>Duration of SCI: mean/ range (years)</th>
<th>n of patients</th>
<th>c/i SCI</th>
<th>Ejaculation in c/i SCI patients</th>
<th>Data source</th>
<th>Rhythmic forceful/ dribbling</th>
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<td>10/8</td>
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unk, unknown; nd, not detailed; nt, not tested; RF, rhythmic forceful; Dr, dribbling; c/i, complete/incomplete.
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<tr>
<th>First author/country</th>
<th>Age: mean/range (years)</th>
<th>SCI classification/individual data</th>
<th>Testing of spinal reflex arcs</th>
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<th>n of patients</th>
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</table>

In all the studies ejaculation occurred in laboratory conditions. unk, unknown; nd, not detailed; nt, not tested; RF, rhythmic forceful; Dr, dribbling; c/i, complete/incomplete; PVS, penile vibratory stimulation.

*Settings of the device used to perform PVS in accordance with optimal settings (amplitude 2.5 mm, frequency 100 Hz) as specified by Sansksen et al. (1994).

**Midodrine prior to PVS for all patients in Soler (2007) and for 10 patients in Courtois (2008).
55.6% (n = 18, CI 33.7–75.5) in patients with incomplete SCI (P = 0.004; Piera, 1973). For the remaining five patients, the occurrence of ejaculation according to the completeness of the injury was not specified (Rawicki and Hill, 1991).

### Comparison of ejaculation rates according to the type of stimulation in patients with complete SCI

The ejaculation rate during masturbation following i.t. prostigmine: 56.1% (n = 132, CI 47.5–64.2) was significantly higher than during masturbation following s.c. physostigmine: 45.1% (n = 233, CI 38.8–51.5, P = 0.05). After failure of masturbation or coitus, without the aid of medications or devices, the salvage manoeuvre of masturbation following i.t. prostigmine or s.c. physostigmine had a significantly higher ejaculation rate: 54.7% (n = 309, CI 49.1–60.2) than the salvage manoeuvre of PVS: 45.8% (n = 542, CI 41.6–50, P = 0.013).

The ejaculation rate during masturbation following i.t. prostigmine or s.c. physostigmine was significantly higher when AchE inhibitors were used after failure of masturbation or coitus without the aid of medications or devices: 54.7% (n = 309, CI 49.1–60.2), than when a first salvage manoeuvre using PVS failed: 17.9% (n = 56, CI 9.8–30; P < 0.0001).

### Impact of the duration of SCI on ejaculation

According to grouped (Horner et al., 1948; Zeitlin et al., 1957; Money, 1960; Hohmann, 1966; Jackson, 1972; Morley et al., 1979; Francois et al., 1980; Brindley, 1981; Sjogren and Egberg, 1983; Beretta et al., 1989; Alexander et al., 1993; Tas et al., 2007; Courtois et al., 2008; Brackett et al., 2010a) or individual (Money, 1960; Jackson, 1972; Morley et al., 1979; Brindley, 1981) data, the ejaculation rate in response to masturbation or coitus without the aid of medications or devices was not significantly correlated with the duration of SCI (beta = −0.01, CI −0.04–0.015, P = 0.4 and beta = 0.01, CI −0.01–0.03, P = 0.27, respectively). According to grouped (Francois et al., 1980; Brindley, 1981; Sarkarati et al., 1987; Beretta et al., 1989; Egon et al., 1994; Odum et al., 1995; Bird et al., 2001; Sonksen, 2003; Hamid et al., 2006; Soler et al., 2007; Courtois et al., 2008; Brackett et al., 2010a) or individual (Brindley, 1981; Odum et al., 1995) data, the ejaculation rate in response PVS was not significantly correlated with the duration of SCI (beta = −0.01, CI −0.12–0.1, P = 0.89 and beta = −0.02, CI −0.11–0.07, P = 0.68, respectively). An assessment of the impact of the duration of SCI on the ejaculation rate in response to masturbation following i.t. prostigmine or s.c. physostigmine could not be conducted because no data were available.

### Ejaculation rates according to the status of the spinal ejaculation centres in patients with complete SCI

#### T12–S5 segments

Data were retrieved from six studies (Piera, 1973; Grossiord et al., 1978; Chapelle et al., 1983a, 1988, 1993; Egon et al., 1994). PVS was used in two studies (Piera, 1973; Egon et al., 1994). In this subset of patients the ejaculation rate was 0% (n = 21, CI 0–13.5) when the lesion extended from T12 to S5 and 73.6% (n = 53, CI 60.3–83.7) when the T12–S5 segments were infralesional (P < 0.0001). Masturbation

### Table III Ejaculation during masturbation following intrathecal prostigmine or subcutaneous physostigmine.

<table>
<thead>
<tr>
<th>First author/country</th>
<th>Age: mean/ range (years)</th>
<th>SCI classification/ individual data</th>
<th>Testing of spinal reflex arcs</th>
<th>Duration of SCI: mean/ range (years)</th>
<th>n of patients</th>
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<th>Ejaculation in c/i SCI patients</th>
<th>Rhythmic forceful/dribbling</th>
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<td>Upper and lower limit/yes</td>
<td>At each segment</td>
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<td>At each segment</td>
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<td>5</td>
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<td>unk</td>
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</tbody>
</table>

In all the studies ejaculation occurred in laboratory conditions. unk, unknown; nd, not detailed; nt, not tested; RF, rhythmic forceful; Dr, dribbling; c/i, complete/incomplete.
following i.t. prostigmine or s.c. physostigmine in the case of failure of masturbation or coitus without the aid of medications or devices was used in the four remaining studies (Grossiord et al., 1978; Chapelle et al., 1983a; 1988, 1993). In this subset of patients the ejaculation rate was 0% ($n = 51$, CI 0–8.4) when the lesions extended from T12 to S5 and 90.8% ($n = 87$, CI 82.7–95.5) when the T12–S5 segments were infralesional ($P < 0.0001$). Masturbation following i.t. prostigmine or s.c. physostigmine was used in four studies after failure of masturbation or coitus without the aid of medications or devices (Grossiord et al., 1978; Chapelle et al., 1983a, 1988, 1993). In this subset of patients, the ejaculation rate was 4.9% ($n = 61$, CI 1.1–14) when the lesion encompassed the T12–L2 segments and 91% ($n = 89$, CI 83–95.6) when the T12–L2 segments were infralesional ($P < 0.0001$).

### T12–L2 segments

Data were retrieved from five studies (Grossiord et al., 1978; Chapelle et al., 1983a, 1988, 1993; Egon et al., 1994). PVS was used in one study (Egon et al., 1994). In this subset of patients the ejaculation rate was 0% ($n = 5$, CI 0–48.9) when the lesions encompassed the T12–L2 segments and 90% ($n = 30$, CI 73.6–97.3) when the T12–L2 segments were infralesional ($P < 0.0001$). Masturbation following i.t. prostigmine or s.c. physostigmine was used in four studies after failure of masturbation or coitus without the aid of medications or devices (Grossiord et al., 1978; Chapelle et al., 1983a, 1988, 1993). In this subset of patients, the ejaculation rate was 4.9% ($n = 61$, CI 1.1–14) when the lesion encompassed the T12–L2 segments and 91% ($n = 89$, CI 83–95.6) when the T12–L2 segments were infralesional ($P < 0.0001$).

### S2–S4 segments

Data were retrieved from six studies. PVS was used in two studies (Brindley, 1981; Egon et al., 1994). In this subset of patients the ejaculation rate was 0% ($n = 4$, CI 0–54.6) when the lesion encompassed the S2–S4 segments and 76.6% ($n = 47$, CI 62.6–86.6) when the S2–S4 segments were infralesional ($P = 0.006$). After failure of masturbation or coitus without the aid of medications or devices, masturbation following i.t. prostigmine or s.c. physostigmine was used in four studies (Grossiord et al., 1978; Chapelle et al., 1983a, 1988, 1993). In this subset of patients the ejaculation rate was 30.8% ($n = 26$, CI 16.3–50.2) when the lesion encompassed the S2–S4 segments and 67.3% ($n = 153$, CI 59.5–74.3) when the S2–S4 segments were infralesional ($P = 0.001$).

### Characterization of ejaculation

The data presented in this review provide additional information about the characterization of ejaculation occurring during PVS or during...
masturbation following i.t. prostigmine or s.c. physostigmine. Normal ejaculation was described, depending on the authors, as propelled, intermittent pulsatile, saccadic, rhythmic forceful or as prior to SCI. In the case of emission without contribution of the somatic centres, ejaculation was described as quiet emission, dripping or emanation of semen without expulsion or dribbling. In order to simplify, we qualified ejaculation as rhythmic forceful or dribbling.

Characterization of ejaculation as rhythmic forceful or dribbling was provided in nine studies (Zeitlin et al., 1957; Comarr, 1970; David et al., 1977; Grossiord et al., 1978; Francois et al., 1980; Brindley, 1981; Beretta et al., 1989; Oates, 1990; Alexander et al., 1993). Ejaculation occurred during masturbation or coitus without the aid of medications or devices. Grey boxes represent the weight of individual studies and the dashed line represents the overall ejaculation rate using a random effect model. PVS, penile vibratory stimulation.

Figure 8 (a) The ejaculation rate in patients with complete or incomplete SCI during masturbation following intrathecal prostigmine or subcutaneous physostigmine after ejaculation failure of masturbation or coitus, without the aid of medications or devices. Grey boxes represent the weight of individual studies and the dashed line represents the overall ejaculation rate using a random effect model. (b) The ejaculation rate in patients with complete or incomplete SCI during masturbation following intrathecal prostigmine or subcutaneous physostigmine after PVS failure. Grey boxes represent the weight of individual studies and the dashed line represents the overall ejaculation rate using a random effect model. PVS, penile vibratory stimulation.

Assessment of the existence of an SGE

Ejaculation rates as a function of the lesional status of the L2–S1 segments

There were four studies (Brindley, 1984, Ohl et al., 1996, Bird et al., 2001, Sonksen, 2003), which evaluated ejaculation following PVS. Unfortunately, i.t. was not possible to separate the results of patients with incomplete and complete SCI in any of these studies. Reflex hip flexion (RHF; L2) in response to nociceptive stimulation of the sole of the foot (S1) only occurs if the L2–S1 segments are infralesional. The ejaculation rate was 25% (n = 88, CI 17.1–35) in patients without RHF and 75% (n = 216, CI 68.8–80.3) in patients with RHF (P < 0.0001).

Ejaculation rates as a function of the lesional status of each spinal segment

In only four studies, the spinal reflex arcs of each segment were tested in order to determine the upper and lower limits of the lesion in complete SCI patients (Grossiord et al., 1978; Chapelle et al., 1983a, 1988, 1993). In these studies masturbation or coitus without the aid of medications or devices failed in all patients. Ejaculation was been attempted by masturbation following i.t. prostigmine or s.c. physostigmine and occurred in 56% of patients (n = 207, CI 49.2–62.6).

By pooling these data, ejaculation rates were calculated depending on the status of each spinal segment, i.e. supra lesional thus intact, injured or infra lesional (Fig. 9). When a segment was intact, all the segments above were by definition intact and the segments below could be intact, injured or infra lesional. When a segment was injured, the segments above could be injured or intact and the segments below could be injured or infra lesional. When a segment was infra lesional, the segments above could be infra lesional, injured or intact and all the segments below were by definition infra lesional.

Intact lower thoracic and upper lumbar segments were associated with a high probability of ejaculation (Fig. 9a). There was a trend for a maximal ejaculation rate when segment L2 and/or L3 and/or L4 were intact (Fig. 9b). There was no patient with an upper limit of the lesion located below L5. Complete lesion of a spinal segment below T10 was associated with a steep decrease in the ejaculation rate with the lowest rate observed with complete lesion of L3 (Fig. 9b). Considering the infralesional segments, the more cranial the lower limit of the lesion, the higher the likelihood of ejaculation with a maximum ejaculation rate when L2 and/or above segments were infralesional (Fig. 9c).
Bivariate analysis yielded that the ejaculation rate was strongly dependent on the number of T12–L2 segments with complete injury. Ejaculation rates ranged from 86% (n = 93, CI 77.4–91.8) to 4.9% (n = 61, CI 1.1–14) depending on the number of completely injured segments between T12 and L2, 0 to 3, respectively (P < 0.0001). We therefore performed a stratified bivariate analysis to assess the impact of the lower limit of the lesion on the ejaculation rate, controlling for the number of T12–L2 segments with complete lesions (Table IV). When there was a complete lesion of 0 or 1 of the T12–L2 segments (Groups 0 and 1), the ejaculation rate was significantly lower in patients with a lower limit at L3 or below, than in patients with a lower limit above L3 (P < 0.0001 and P = 0.0007, respectively). When there were complete lesions of 2 or 3 of the T12–L2 segments (Groups 2 and 3), there was no significant difference in the ejaculation rate between patients with a lower limit at the L3 segment or below compared with those with a lower limit above L3. A stratified bivariate analysis to assess the impact of the upper limit of the lesion on the ejaculation rate, controlling for the number of S2–S4 segments with complete lesions could not be conducted because of the small number of patients with injuries restricted to the lumbo-sacral segments.

The number of patients with complete SCI extending from T12, L1 or L2–L3, L4 or L5 was again too small to compare the ejaculation rates as a function of the lower limit of the lesion. It was thus not possible to correlate ejaculation impairment with the number of L3–L5 segments injured.

**Discussion**

Over the last decades, anejaculation in SCI patients has remained a major issue with sexual function being the main problem in these patients (Anderson, 2004; Simpson et al., 2012).

While considerable progress has been achieved regarding sperm retrieval with techniques which have evolved over time, the rate of ejaculation during masturbation or coitus without the aid of medications or devices is still very low, i.e. 16.0% overall, 11.8% in patients with complete and 33.2% in patients with incomplete SCI. These results are in line with ejaculation rates reported in previous reviews (Talbot, 1955; Bors and Comarr, 1960; Tsuji et al., 1961; Uyttendaele et al., 1979; Brackett, 1999; Sonksen and Ohi, 2002). This means that the vast majority of SCI males need assistance to father children or simply to ejaculate for reasons other than procreation (Anderson et al., 2007). The use of PVS to elicit ejaculation and retrieve sperm ex copula increases the rate of ejaculation to 52.1% overall. It appears that PVS-induced ejaculation occurs slightly more easily when the SCI is incomplete (52.8%) compared with complete (47.4%), although this difference was not statistically significant. The ejaculation rate with PVS did not significantly improve with the use of optimal vibration parameters (2.5 mm amplitude, 100 Hz frequency; Sonksen et al., 1994). In the landmark study in 1994 by Sonksen et al., the same group of patients underwent the same PVS procedure with two different amplitudes but at the same frequency. In the 11 selected studies using non-optimal parameters for PVS, there was considerable disparity regarding the vibratory amplitude and frequency, the upper limits and completeness of the lesion, the duration of SCI and the medication at the time of PVS. Therefore, the present results are not in contradiction with Sonksen’s data (Sonksen et al., 1994) and may only reflect the difficulties inherent in the comparison of different studies. Prior to the increase in the use of the PVS technique with the development of the FerticareR device, AchE inhibitors, i.e. i.t. prostigmine and s.c. physostigmine were used when patients were unable to ejaculate during masturbation or sexual intercourse. Conversely to prostigmine, which requires i.t. administration to be effective, physostigmine crosses the blood brain barrier allowing s.c. delivery.
The upper limit of complete SCI was segment L3 or above in all patients (Grossiord et al., 1978, Chapelle et al., 1983a, Chapelle et al., 1988, Chapelle et al., 1993). nb, number.

(Bullock et al., 1946; Togashi et al., 1994). In patients with complete SCI, after ejaculation failed to occur during masturbation or coitus without the aid of medications or devices, AchE inhibitors were found to be a more effective salvage manoeuvre than PVS with ejaculation rates of 54.7 versus 45.8%, respectively. In patients with incomplete SCI, AchE inhibitors were also a more effective salvage manoeuvre than PVS with ejaculation rates of 78.1 versus 53.0%, respectively. When AchE inhibitors were used as a second salvage manoeuvre, i.e. after failure of PVS, the ejaculation rate was 37.6% with a greater efficacy in patients with incomplete SCI. Accordingly, AchE inhibitors can be useful for some PVS non-responders. However, neither i.t. prosta-mogenic nor s.c. physostigmine are currently used because of safety issues, particularly AD, as previously mentioned.

The mechanism of action of AchE inhibitors in ejaculation is not well understood. The fact that prosta-mogenic elicits or facilitates ejaculation when delivered it but not systematically (Guttmann, 1949) clearly indicates a spinal rather than peripheral mechanism of action. This view is further supported by experimental data. In rat spinal cord slices, prostigmine activates presynaptic M1 muscarinic subtype receptors that increase the release of noradrenalin and enhance the activity of autonomic preganglionic neurons located in the IML (Takahashi and Buccafusco, 1992; Umeda et al., 2006). Activation of sympathetic and parasympathetic neurons innervating the anatomical structures involved in ejaculation facilitates ejaculation. In addition, AchE inhibitors, which augment Ach bioavailability, may increase cholinergic transmission in a spinal network which integrates sensory, motor and autonomic information. Such a network has been described in the rat comprising cholinergic neurons with cell bodies located around the central canal (lamina X) and terminals in the IML as well as in the dorsal and ventral horns (Navar-ach and Lewis, 1970; Borges and Iversen, 1986). The lamina X cholinergic neurons are most numerous at the lumbar enlargement of the spinal cord in the rat and form clusters of cells with an organization which resembles the SGE (Fig. 1). Whether those neurons are part of the SGE and whether their activation triggers or facilitates ejaculation remains to be demonstrated. In addition, physostigmine and prostigmine may concomitantly increase the amount of Ach in preganglionic and postganglionic axon terminals (Kwok and Collier, 1982; Brunton et al., 1995).

In summary, AchE inhibitors may activate cholinergic pathways, enhancing the activity of sympathetic preganglionic neurons but also upstream, in the medial part of lamina VII and in lamina X of the spinal cord where the SGE is located. This might explain the spontaneous ejaculations which occur following i.t. prostigmine in SCI patients (Guttmann and Walsh, 1971).

One limitation of this systematic review is its relative lack of exhaustiveness. The ejaculation rates in the different types of SCI were only retrieved from articles which provided details of the neurological characterization of the SCI. Nevertheless, because of the rather low variability of the data across the selected studies, it is unlikely that including more articles would have changed the main results of this review.

Another limitation is the lack of assessment of the role of AD in failure of ejaculation whatever the type of stimulation used. Indeed, AD can prevent the achievement of ejaculation. Episodes of AD and the associated increase in blood pressure, which are not usually reported during sexual stimulation (Lindan et al., 1980), are common during sperm retrieval procedures, especially in the case of cervical or high thoracic SCI (McBride et al., 2003; Sheel et al., 2005; Elliott and Krasikoulo, 2006; Courtois et al., 2008a; Eklund et al., 2008). In the selected papers, it was not possible to differentiate between failure to ejaculate because of the SCI or because the stimulation had to be stopped because of AD.

Another weakness of this review is the lack of information regarding the concomitant treatments of the SCI patients enrolled in the studies. Centrally acting drugs (Giuliano and Clement, 2012) including the selective serotonin reuptake inhibitors for depression (Waldinger et al., 1998; Giuliano, 2007) and the analgesic tramadol (Bar-O et al., 2012; Giuliano, 2012) can delay and sometimes abolish ejaculation. The adrenoceptor blocking agent tamsulosin and more recently silodosin, which are
prescribed off-label for bladder sphincter dyssynergia in SCI patients, can be responsible for anejaculation (Hellstrom and Sikka, 2006; Masumori et al., 2009). Intradermous botulinum toxin injections for the treatment of neurogenic detrusor overactivity have recently been reported to cause retrograde ejaculation and to decrease total semen volume (Caremel et al., 2012). Conversely, phosphodiesterase type 5 inhibitors often prescribed since 1998 for the treatment of erectile dysfunction in SCI patients have been reported to slightly increase the occurrence of ejaculation during masturbation or coitus without the aid of medications or devices in this population (Giuliano et al., 1999; Giuliano et al., 2007; Giuliano et al., 2008). To summarize, the side effects of medication on ejaculation in SCI patients have not been addressed in the present review because this information was missing from most of the included studies.

In this review, we focused on mechanical, i.e. masturbation, coitus without the aid of medications or devices, or PVS, or pharmacological methods to elicit ejaculation. Although poorly reported, supraspinal stimulation, i.e. erotic thoughts or erotic movie watching can induce psychogenic emission defined as a ‘whitish and viscous substance expelled or dribbled (…) but without any peripheral stimulation’ (Courtois et al., 1993). If the upper limit of SCI is located below T12, psychogenic emission can occur. Conversely, when elicited by PVS, ejaculation requires at least partial preservation of afferent nerves to convey excitatory stimuli from the glans or perineal region to activate the spinal centres (Talbot, 1949; Bors and Comarr, 1960; Comarr, 1970; Chapelle et al., 1982; Brindley, 1984; Kinsey et al., 1998). Only one report which specifically evaluated the occurrence of psychogenic emission found that almost half of the patients with an upper limit of SCI located below L2, mostly incomplete, were able to have psychogenic emissions which could contain motile spermatozoa. Whether this emission was rhythmic or dribbling was unfortunately not specified (Courtois et al., 1993).

Despite a few optimistic reports (Egon et al., 1994; Lochner-Ernst et al., 1997; Sonksen, 2003), the results of the present systematic review showed that there is still almost a 50% failure rate of PVS to retrieve sperm during antegrade ejaculation. PVS is the only technique that allows intravaginal insemination at home for couples, without any further medical assistance. The possibility of conception, however, requires at least partial preservation of afferent nerves to convey excitatory stimuli from the glans or perineal region to activate the spinal centres. In these patients, one or two of the T12–L2 segments where the sympathetic ejaculation centres are located were intact. They were damaged (Chapelle et al., 1982) as T12–L2 has been obtained from a single study with no more than 30 patients. More data in this subset of patients are warranted. The ejaculation rate during masturbation or coitus without the aid of medications or devices was significantly lower in the case of complete lesions of the T12–S5 segments than when these segments were infralesional. When complete SCI is located above the T12 segment, PVS or pharmacological stimulation combined with masturbation are required for ejaculation because of the loss of supraspinal excitatory influences. This reinforces the concept of a spinal network located within the T12–S5 segments which, when properly stimulated, triggers normal ejaculation despite the lack of brain influences.

**Ejaculation rates according to the status of the T12–S5 segments**

**T12–S5 segments as a whole**

In response to PVS or during masturbation following i.t. prostigmine or s.c. physostigmine, the ejaculation rate was (i) 0% in patients with complete lesions of the T12–S5 segments and (ii) 73.6 and 90.8%, respectively when the T12–S5 segments were infralesional. When complete SCI is located above the T12 segment, PVS or pharmacological stimulation combined with masturbation are required for ejaculation because of the loss of supraspinal excitatory influences. This reinforces the concept of a spinal network located within the T12–S5 segments which, when properly stimulated, triggers normal ejaculation despite the lack of brain influences.

**T12–L2 segments**

The ejaculation rate in laboratory conditions were dramatically decreased, close to zero, in patients with complete injury of the T12–L2 segments. Conversely, when these segments were infralesional, 9 out of 10 patients were able to ejaculate by using PVS or when masturbation followed i.t. prostigmine or s.c. physostigmine. It is noteworthy that the 90% ejaculation rate in patients with infralesional segments T12–L2 has been obtained from a single study with no more than 30 patients. More data in this subset of patients are warranted. The ejaculation rate during masturbation or coitus without the aid of medications or devices was significantly lower in the case of injury of the T12–L2 segments than when these segments were infralesional (data not shown). These data confirm the necessity for the T12–L2 segments to be infralesional in order for ejaculation to occur.

This is further supported by a report from Chapelle et al. (1988) in which three patients with complete SCI extending from the L1 or L2 to S5 segments ejaculated during masturbation following s.c. physostigmine. In these patients, one or two of the T12–L2 segments where the sympathetic ejaculation centres are located were intact. They were thus under supraspinal control, allowing psychogenic stimulation to elicit dribbling ejaculation. The same authors claimed that ejaculation will only be prevented during masturbation following i.t. prostigmine or s.c. physostigmine if at least two of the T12, L1 and L2 segments are damaged (Chapelle et al., 1982).

**S2–S4 segments**

The ejaculation rate in laboratory conditions was significantly lower in the case of complete lesions of the S2–S4 segments than when these segments were infralesional. However, this difference was less obvious than when comparing the complete lesion with infralesional location of the T12–L2 segments. Conversely, the ejaculation rate during masturbation or coitus without the aid of medications or devices was higher in the case of lesions of the S2–S4 segments than when these segments were infralesional (data not shown). Such an apparent contradiction between data retrieved in laboratory conditions and self-reported may be explained by the lack of reliability of data self-reported by the
Four studies have highlighted the necessity of the L2–S1 segments to be infra-lesional, psychogenic emission can occur. The S2–S4 segments must be infra-lesional for rhythmic forceful ejaculation to occur in response to any kind of stimulation.

**Assessment of the existence of an SGE**

Four studies have emphasized the necessity of the L2–S1 segments to be infra-lesional for PVS elicited ejaculation to occur (Brindley, 1984; Ohl et al., 1996; Bird et al., 2001; Sonksen, 2003). The status of these segments was assessed by scratching the sole of the foot (SFS, S1 segment) to verify the presence of RHF (RHF, L2 segment). For this polysynaptic reflex to occur, the L2–S1 segments must be at least partially intact since somaticreflexes occur at these levels and the intraspinal pathway is conveyed through the L3, L4 and L5 segments (Faganel and Dimitrijevic, 1982). A quarter of the patients with absent RHF after SFS could ejaculate. The above mentioned studies mostly included patients with incomplete SCI in whom the intraspinal L2 to S1 pathways involved in PVS-elicited ejaculation might not have been completely disrupted. Brindley considered that a spinal reflex arc between L2 and S1 could support the coordinated activation of the sympathetic, parasympathetic and somatic centres and suggested that these segments act as a sacroccocygeal intersegmental reflex circuit (Brindley, 1981). We suggest that the L2–S1 segments may well be the location of an SGE in man rather than a simple intersegmental spinal reflex arc.

In rats, the injection of the neurotoxin saporin conjugated to a substance P analogue responsible for a selective lesion of SGE interneurons in laminae X and VII of L3 and L4 resulted in the abolition of ejaculation without impairment of the other components of male sexual behaviour (Truitt and Coolen, 2002). In addition, in rats, selective lesions of the SGE interneurons disrupt the rhythmic bursting of the bulbospongious muscle following dorsal penile nerve, urethral or pharmacological stimulation (Staudt et al., 2012). In order to know whether such a neuronal organization also exists in humans, we examined ejaculation occurrence as a function of the location of SCI, focusing on the putative location of an SGE, i.e. the L3–L5 segments.

This hypothesis is based on the location of the SGE in rats, in which the physiology of ejaculation is similar to humans (Giuliano et al., 2010), and accounts for interspecies differences in metamerization. Even though some authors have recently speculated about the existence of an SGE in humans (Alexander and Rosen, 2008; Everaert et al., 2010; Courtois et al., 2011), to our knowledge, such evidence has not been yet provided.
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spared, thereby allowing ejaculation to occur. It is noteworthy that the data in favour of the existence of an SGE in humans have been retrieved from studies in which ejaculation was elicited during masturbation following i.t. prostaglandin or s.c. phystostigmine. From a pharmacological perspective, the effect of AChE inhibitors on ejaculation could be dual: (i) potentiation of the excitatory action of the putative SGE on autonomic and somatic pathways controlling the peripheral events leading to ejaculation and (ii) direct activation of those pathways. It would have been more convincing if the same results in favour of the existence of an SGE had come from PVS data. Unfortunately, such results are not currently available.

Conclusion

This systematic review of the data available in SCI men thus confirms the role of the already known spinal ejaculation centres located at the level of the T12—L2 and S2—S4 segments. It also supports the existence of an SGE in humans which is likely to be located at the level of the L3, L4 and L5 segments.

Our understanding of the human spinal physiology of ejaculation needs further improvement. It is essential to provide definite evidence for the existence of an SGE in man. This would allow the transposition of experimental results from rats to humans and open new avenues in pharmacological research for the treatment of various ejaculatory disorders not only including anejaculation in SCI patients but also delayed and premature ejaculation. Restoring ejaculation in SCI patients would allow procreation to occur with little or no medical assistance and better sexual achievement aside from any procreative considerations.

Authors’ roles

C.C. was responsible for data extraction, critical appraisal, data analysis, data interpretation and writing of the report. S.B. and F.G. were responsible for data analysis, data interpretation and writing of the report. P.D. contributed to data interpretation and gave his specialized clinical feedback. P.C. and J.B. contributed to the writing of the report. S.B. and F.G. C.C. was responsible for data extraction, critical appraisal, data analysis, data interpretation and writing of the report. S.B. and F.G.

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Appendix


Muscle Function Grading

0  =  total paralysis
1  =  palpable or visible contraction
2  =  active movement, full range of motion (ROM) with gravity eliminated
3  =  active movement, full ROM against gravity
4  =  active movement, full ROM against gravity and full resistance in a muscle specific position.
5  =  (normal) active movement, full ROM against gravity and full resistance in a muscle specific position expected from an otherwise unimpaired person.
NT= not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contraction of >50% of the range of motion).

ASIA Impairment (AIS) Scale

☐ A  =  Complete, No sensory or motor function preserved in the sacral segments S4-S5.
☐ B  =  Sensory Incomplete, Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5 (light touch, pin prick at S4-S5 or deep and pressure (DAP), AND no motor function is preserved more than three levels below the motor level on either side of the body.
☐ C  =  Motor Incomplete, Motor function is preserved below the neurological level**, and more than half of key muscle functions below the single neurological level of injury (NSLI) have a muscle grade less than 3 (Grade 0-2).
☐ D  =  Motor Incomplete, Motor function is preserved below the neurological level**, and all or joint half of key muscle functions below the NSLI have a muscle grade less than 3 (Grade 0-2).
☐ E  =  Normal, If sensation and motor function as tested with the SNISCS are normal in all segments, and the patient had no deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.

**For an individual to receive a grade of C or D, i.e., motor incomplete states, they must have either (a) voluntary and involuntary contraction or (b) normal sensory sparing with sparing of motor function more than three levels below the motor level on either side of the body. The Standards at the time allows even non-key muscle function more than 3 levels below the motor level to be used in determining motor incomplete states (AIS-B versus C).

Steps in Classification

The following order is recommended in determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
2. Determine motor levels for right and left sides.
3. Determine the single neurological level. Pick is the lowest segment where motor and sensory function is normal on both sides, and is the most cephalad of the sensory and motor levels determined in stage 1 and 2.
4. Determine whether the injury is Complete or Incomplete. (i.e. absence or presence of sacral sparing) if voluntary and contraction = No or AIS all S4-5 sensory scores = 0 AND deep and pressure = No, then injury is COMPLETE. Otherwise, injury is incomplete.
5. Determine ASIA Impairment Scale (AIS) Grade.

NO

Injury Caudal?

IF YES, AIS-A and can record ZFP (lowest dermatome or motor on each side with some preservation)

IF NO, AIS-B (Year-voluntary and contraction OR motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)

Any at least half of the key muscles below the single neurological level graded 3 or better?

NO

AIS=C

YES

AIS=D

If contraction and motor function normal in all segments, AIS-E.

Note: AIS-E is used in follow-up testing when an individual with a documented SCI has recovered normal function. If it is first testing or deficits are found, the individual is neurologically intact; the ASIA Impairment Scale does not apply.