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

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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.

METHODS: Studies were identified from Embase, PubMed, EBSCOhost and Cochrane Library. Studies were eligible when they specify the occurrence of antegrade ejaculation as a function of the neurological characterization of SCI. Studies were excluded when ejaculation was elicited by rectal electrical stimulation or when ejaculation could not be discriminated from climax. Meta-analyses were performed to assess the reference ejaculation rates for each procedure used to elicit ejaculation, i.e. masturbation or coïtus, penile vibratory stimulation (PVS) or acetylcholine esterase (AchE) inhibitors prior to masturbation. Subgroup analyses were performed according to the procedure used to elicit ejaculation on (i) the completeness of the SCI and (ii) the upper and lower limits of the SCI. To assess the existence of an SGE, the effect of concurrent lesions of different spinal segments was assessed by means of a stratified bivariate analysis.

RESULTS: From 523 studies, 45 were selected ($n = 3851$). Ejaculation occurred in response to masturbation or coïtus, PVS or AchE inhibitors followed by masturbation in, respectively, 11.8% ($n = 1161$), 47.4% ($n = 597$) and 54.7% ($n = 309$) of patients with complete SCI and in, respectively, 33.2% ($n = 343$), 52.8% ($n = 305$) and 78.1% ($n = 32$) of patients with incomplete SCI. Ejaculation, in the case of complete lesion of the sympathetic centres (T12 to L2), of the parasympathetic and somatic centres (S2–S4) or of all spinal ejaculation centres (T12 to S5) occurred in response to PVS in none of the patients (respectively, $n = 5$, $n = 4$ and $n = 21$) and in response to AchE inhibitors followed by masturbation in 4.9% ($n = 61$), 30.8% ($n = 26$) and 0% ($n = 16$) of the patients, respectively. Ejaculation in response to PVS or AchE inhibitors prior to masturbation was rhythmic forceful in 97.9% ($n = 48$) of the patients with complete lesion strictly above Onuf's nucleus (segments S2–S4). Complete lesion of the S2–S4 segments precluded the occurrence of rhythmic forceful ejaculation ($n = 5$). Controlling for the number of the injured segments between T12 and L2, the ejaculation rate sharply decreased when the lesion extended to the L3 segment and below.

CONCLUSIONS: The results reinforce the crucial roles of the spinal sympathetic and parasympathetic centres for emission and the somatic centre for expulsion. The spinal segments between L2 and S2 is more than a pathway to connect the ejaculation centres and likely harbours an SGE in man located in the L3, L4 and L5 segments.

Key words: paraplegia / quadriplegia / fertility / spinal generator of ejaculation / physiology

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 pelvi-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 spinothalamic 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 that specifically controls 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 T12–L2 paravertebral sympathetic ganglia (Whitelaw and Smithwick, 1951; Courty and

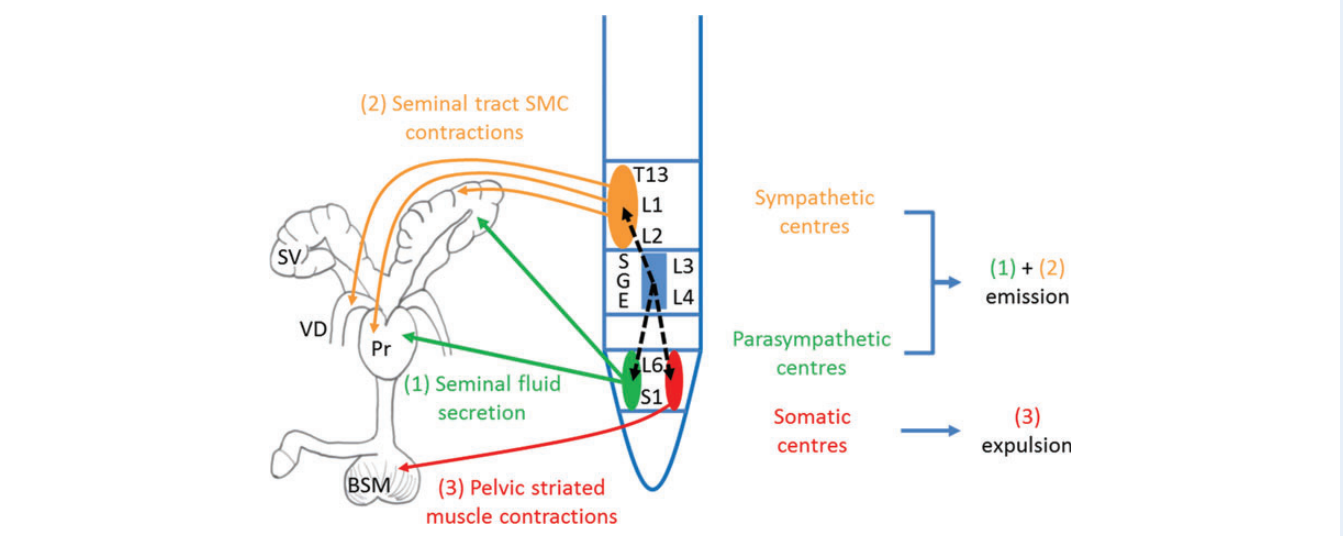

Figure 1 Spinal and peripheral neural control of ejaculation in rats. Once activated the SGE commands and coordinates the activity of: (1) parasympathetic centres which innervate the accessory sex glands (prostate and seminal vesicles) secreting seminal fluid. (2) Sympathetic centres which innervate smooth muscle cells of the seminal tract and the bladder neck. Contraction of the whole seminal tract brings spermatozoa mixed with the seminal fluid to the prostatic urethra. The bladder neck remains closed to prevent the sperm flowing backwards into the bladder (retrograde ejaculation). (3) Somatic centres that innervate the pelvic striated muscles. The external urethral sphincter relaxes and rhythmic contractions of the bulbo spongiosus and ischio cavernosus muscles are responsible for rhythmic forceful expulsion of sperm at the urethral meatus. SMC, smooth muscle cells; VD, vas deferens; SV, seminal vesicle; Pr, prostate; BSM, bulbo spongiosus muscle; SGE, spinal generator of ejaculation.

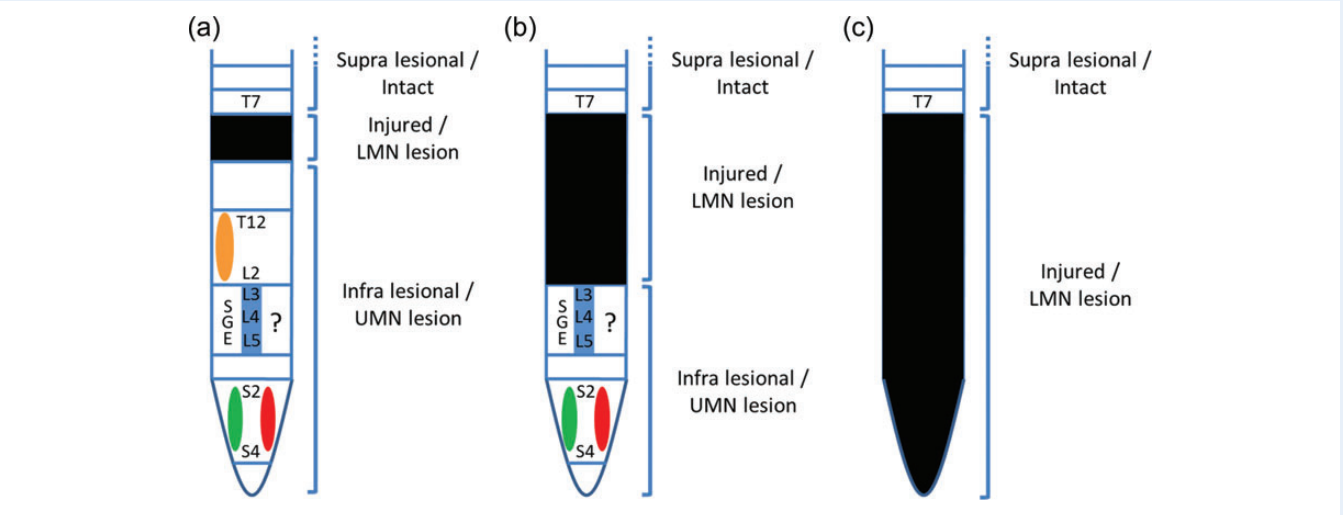

Figure 2 Three spinal cord injuries (SCI) with the same upper limit (T8) but with different lower limits: (**a**) T9; (**b**) L2 and (**c**) S5. SGE, putative spinal generator of ejaculation; T12-L2, sympathetic ejaculation centres; S2–S4, parasympathetic and somatic ejaculation centres. LMN, lower motor neuron lesion (at the level of injury)/UMN, upper motor neuron lesion (below the injury).

Franchebois, 1952; Rose, 1953). 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

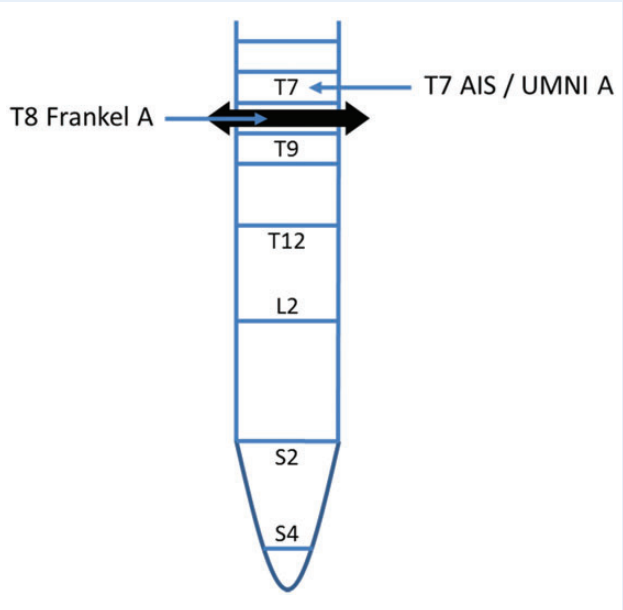

Figure 3 Complete SCI with an upper limit at T8. Comparison between the three SCI classifications: ASIA Impairment Scale (AIS), UMNI and Frankel. T7 AIS = T7 UMNI = T8 Frankel. Letter A indicates complete motor and sensory injury.

the most caudal intact segment for the UMNI 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 nociceptive 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) T9, thus autonomic and somatic ejaculation centres would be infra lesional (Fig. 2a) or

(ii) L2, thus causing direct lesions of the sympathetic ejaculation centres, but the parasympathetic and somatic ejaculation centres would be infra lesional (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 metamerization 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 coïtus. 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, coïtus 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, physostigmine, was then used in SCI patients to facilitate ejaculation induced by masturbation (Chapelle, 1979). The use of this compound was then also stopped because of potential severe AD. Midodrine, an α1-adrenergic receptor agonist registered for the treatment of orthostatic hypotension (Lossnitzer and Letzel, 1983; Wright *et al.*, 1998), increases the rate of

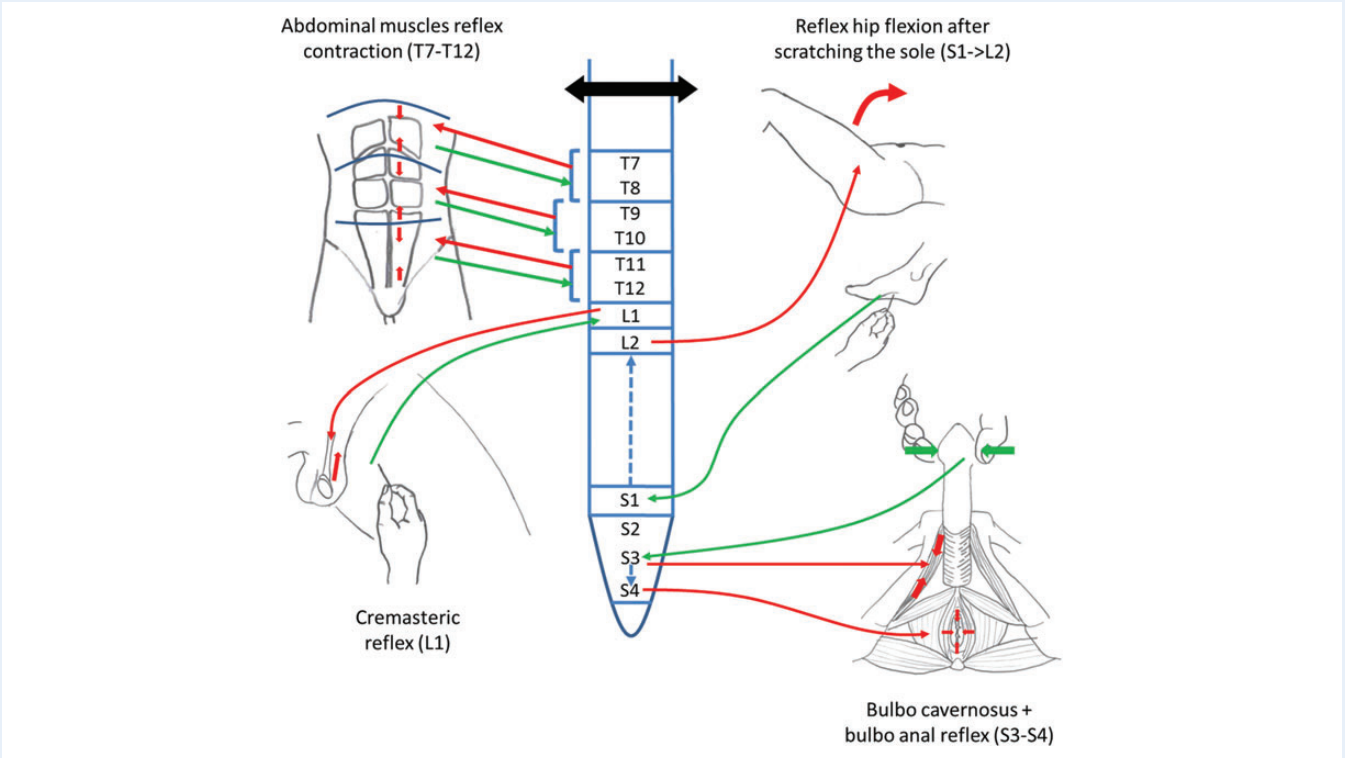

Figure 4 Sacral, lumbar and thoracic testing of spinal reflex arcs relative to motor metamerization to determine the lower limit of the injury (green, sensory afferents; red, motor efferents) in the case of complete SCI. Pinching or pricking upper, intermediate or lower abdominal skin elicits abdominal 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 cavernosus muscle (segment S3) and external anal sphincter (segment S4) contraction.

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

(v) Level of the lesion
(vi) Evaluation of somatic spinal reflex arcs
(vii) Stimulation procedures used to elicit ejaculation
(viii) Rate of ejaculation
(ix) Characterization of ejaculation: rhythmic forceful or dribbling.

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 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 lesional status of the spinal segments.

Reference ejaculation rates were first calculated in patients (i) with complete lesions of the T12–S5 segments and (ii) with lesions strictly located 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 lesional 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 χ^2 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; Zeitlin *et al.*, 1957; Bors and Comarr, 1960; Money, 1960; Comarr, 1970; Guttmann and Walsh, 1971; Jackson, 1972; Piera, 1973; Fitzpatrick, 1974; David *et al.*, 1977; Comarr and Vigue, 1978; Grossiord *et al.*, 1978; Francois *et al.*, 1980; Brindley, 1981; Chapelle *et al.*, 1982; 1983a, Francois *et al.*, 1983; Sjogren and Egberg, 1983; Brindley, 1984; Sarkarati *et al.*, 1987; Chapelle *et al.*, 1988; Beretta *et al.*, 1989; Slot *et al.*, 1989; Szasz and Carpenter, 1989; Oates, 1990; Rawicki and Hill, 1991; Alexander *et al.*, 1993; Egon *et al.*, 1994; Nehra *et al.*, 1996; Ohl *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; Odum *et al.*, 1995), one article was about emotional feelings (Hohmann, 1966) and another one article was about the function of the infra lesional 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 ejaculation 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 coïtus 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 coïtus 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 UMNI 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,

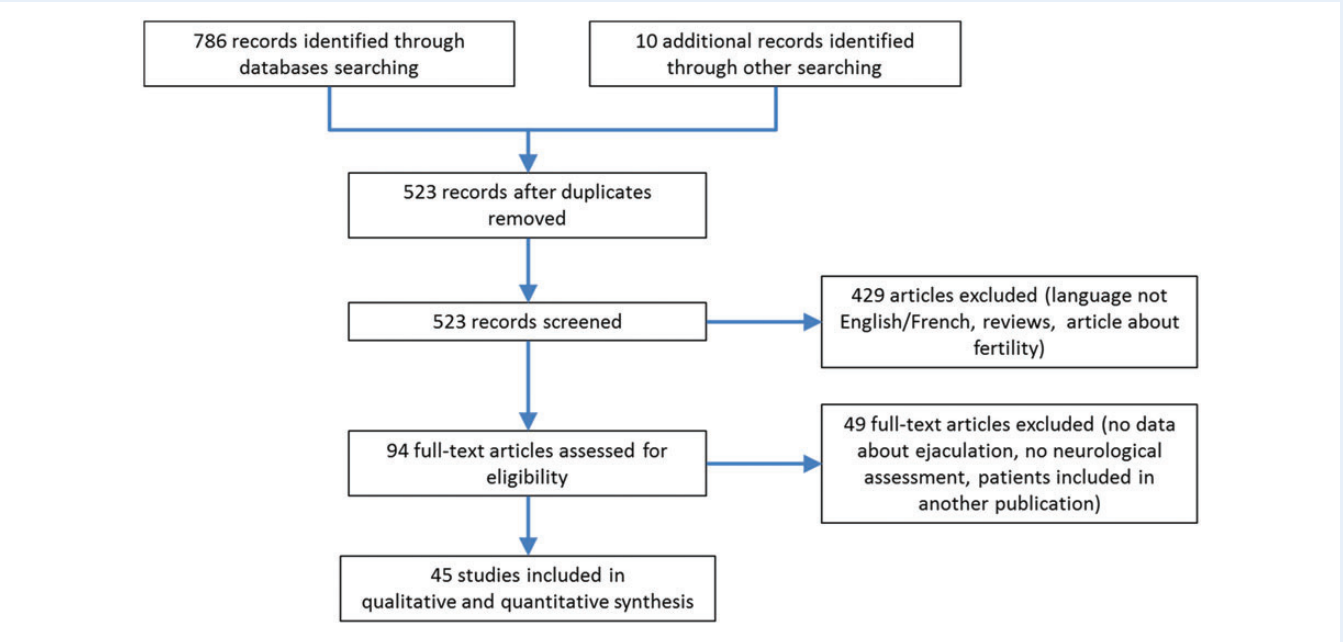

Figure 5 Search strategy flowchart.

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 coïtus 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 coïtus, the overall ejaculation rate was 16.0% (CI 2.5–19.5). It was 11.8% ($n = 1161$, 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; Sjogren 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 1005 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 coïtus 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 1009 patients, the ejaculation rate according to the completeness of the injury was not specified (Sarkarati *et al.*, 1987; 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 coïtus 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 61–89.3) 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.

First author/country	Age: mean/ range (years)	SCI classification/ individual data	Testing of spinal reflex arcs	Duration of SCI: mean/ range (years)	*n* of patients	c/i SCI	Ejaculation in c/i SCI patients	Data source	Rhythmic forceful/ dribbling
Munro, 1948/USA	unk/31–40	Frankel/no	nt	unk	82	47/35	3/5	Self-reported	unk
Horne, 1948/USA	27/21–35	Frankel/yes	nt	3.9/0.75–6	18	10/8	1/2	Laboratory condition	unk
Kuhn, 1950/USA	unk	Frankel/yes	S2–S4/L1	unk/2–unk	25	25/0	2	Self-reported	unk
Zeitlin, 1957/USA	35/21–68	Frankel/no	nt	6/1–38	100	unk	3 (nd)	Self-reported	RF = 3 Dr = 0
Money, 1960/USA	30.4/18–66	Frankel/yes	nt	3.6/0.2–16	14	14/0	0	Self-reported	0
Bors, 1960/USA	unk	Frankel/no	S2–S4	unk	529	396/133	34/46	Self-reported	unk
Hohmann, 1966/USA	36/27–47	Frankel/yes	nt	11/2–17	25	25/0	3	Self-reported	unk
Comarr, 1970/USA	unk/19–74	Frankel/no	S2–S4	unk/0.3–25	150	108/42	6/10	Self-reported	RF = 10 Dr = 6
Jackson, 1972/Canada	unk	Frankel/no	nt	10.7/1–29	20	unk	7 (nd)	Self-reported	unk
Fitzpatrick, 1974/USA	28/18–42	ASIA/yes	nt	unk	12	unk	6 (nd)	Self-reported	unk
David, 1977/Israël	unk/18–33	Frankel/no	S2–S4	unk	16	13/3	1/3	Self-reported	RF = 4
Comarr, 1978/USA	unk	Frankel/no	S2–S4	unk/0.1–26	153	109/44	2/18	Self-reported	unk
Grossiord, 1978/France	unk/18–50	Frankel/yes	Each segment	unk/0.5–unk	113	113/0	31	Self-reported	unk
Morley, 1979/South Africa	33.5/19–70	Frankel/no	nt	9/1–23	18	unk	6 (nd)	Self-reported	unk
Francois, 1980/France	25/16–46	Frankel/no data	nt	5/0.5–18	50	33/17	8 (nd)	Self-reported	unk
Brindley, 1981/UK	35.2/21–44	Frankel/yes	S2–S4	6.2/1–15	9	7/2	1/0	Self-reported	RF = 1
Chapelle, 1982/France	unk/18–50	Frankel/no	nt	unk/0.5–unk	149	149/0	39	Self-reported	unk
Francois, 1983/France	unk	Frankel/no	nt	unk	140	87/53	1/15	Laboratory condition	unk
Sjogren, 1983/Sweden	27/unk	ASIA/no	nt	3/1–unk	21	21/0	7	Self-reported	unk
Brindley, 1984/UK	unk	Frankel/no data	nt	unk/0.5–unk	81	unk	3 (nd)	Self-reported	unk
Beretta, 1989/Italia	25.6/unk	Frankel/no data	nt	6.1/unk	72	30/42	5 (nd)	Self-reported	unk
Slot, 1989/Danemark	27.5/20–63	ASIA/no	nt	unk	38	27/11	9/9	Self-reported	unk
Rawicki, 1991/Australia	unk	Frankel/no	nt	unk	35	unk	4 (nd)	Self-reported	unk
Alexander, 1993/USA	26/18–70	ASIA/no	nt	3.1/0.4–22	38	28/10	4/5	Laboratory condition	RF = 2 Dr = 7
Denys, 1998/France	35.8/29–48	Frankel/yes	S2–S4	unk	5	3/2	0/1	Self-reported	unk
Tas, 2007/Turkey	34.1/21–53	ASIA/no	nt	2.2/0.3–10.58	15	unk	7	Self-reported	unk
Courtois, 2008/Canada	34/18–65	ASIA/no	nt	7/0.25–30	81	40/41	24 (nd)	Laboratory condition	unk
Brackett, 2010/USA	34.1/17–63	UMNI/no data	nt	10/unk	500	unk	43 (nd)	Laboratory condition	unk

unk, unknown; nd, not detailed; nt, not tested; RF, rhythmic forceful; Dr, dribbling; c/i, complete/incomplete.

Table II Ejaculation elicited by PVS.

First author/country	Age: mean/ range (years)	SCI classification/ individual data	Testing of spinal reflex arcs	Duration of SCI: mean/ range (years)	*n* of patients	c/i SCI	Ejaculation in c/i SCI patients	Rhythmic forceful/ dribbling
Piera, 1973/France	unk	No data	T10–S5	unk	101	68/33	12/15	unk
François, 1980/France	25/16–46	Frankel/no	nt	5/0.5–18	50	33/17	22/14	RF = 35 Dr = 1
Brindley, 1981/UK	27.3/18–50	Frankel/yes	S2–S4	6.5/0.5–25	21	15/6	9/3	RF = 12 Dr = 0
François, 1983/France	unk	Frankel/no	nt	unk	140	87/53	48/20	unk
Brindley, 1984/UK	Unk	Frankel/no data	L2–S1	unk/0.5–unk	81	57/24	36/12	unk
Sarkarati, 1987/USA	unk/16–36	Frankel/yes	nt	2.1/0.1–13	34	19/15	7 (nd)	unk
Szasz, 1989/Canada	unk/24–39	ASIA/no	nt	unk/0.8–23	35	21/14	7/4	unk
Beretta, 1989/Italia	25.6/unk	Frankel/no	nt	6.1/unk	102	45/57	29/36	RF = 54 Dr = 11
Oates, 1990/USA	27.5/18–41	unk/no	nt	unk	21	unk	8 (nd)	RF = 8 Dr = 0
Rawicki, 1991/Australia	Unk	Frankel/no	nt	unk	9	unk	4 (nd)	unk
Egon, 1994[a]/France	30/19–54	ASIA/no	T12–L2/S2–S4	6/0.6–16	52	36/16	27/7	unk
Odum, 1995[a] /Denmark	30/21–45	ASIA/yes	nt	7/1–29	12	9/3	6/1	unk
Ohl, 1996[a] /USA	Unk	Frankel/no	L2–S1/S2–S4	Unk	34	29/5	19/3	unk
Nehra, 1996[a] /USA	26.9/23–40	Frankel/no	nt	Unk	78	unk	34 (nd)	unk
Bird, 2001[a] /USA	33.3/17.4–48.2	UMNI/no	L2–S1/S2–S4	10/2–28.8	123	unk	73 (nd)	unk
Sønsksen, 2003[a] /Denmark	28.2/18–44	ASIA/no	T6–T12/L2–S1/S2–S4	5/0.2–39	66	44/22	41 (nd)	unk
Hamid, 2006[a] /UK	35.6/18–56	Frankel/no	nt	10.4/0.5–27	74	41/33	14/23	unk
Soler, 2007[a,b]/France	31.3/unk	ASIA/no	nt	5.3/0.4–unk	158	118/40	70 (nd)	unk
Courtois, 2008[b]/Canada	34/18–65	ASIA/no	nt	7/0.25–30	57	unk	50 (nd)	unk
Brackett, 2010[a] /USA	34.1/17–63	UMNI/no	nt	10/unk	461	unk	249 (nd)	unk
Soler, 2011[a] /France	Unk	ASIA/no	nt	unk/4–20	202	158/44	55/23	unk

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.
[a]Settings of the device used to perform PVS in accordance with optimal settings (amplitude 2.5 mm, frequency 100 Hz) as specified by Sønsksen *et al*. (1994).
[b]Midodrine prior to PVS for all patients in Soler (2007) and for 10 patients in Courtois (2008).

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

First author/ country	Age: mean/ range (years)	SCI classification/ individual data	Testing of spinal reflex arcs	Duration of SCI: mean/ range (years)	*n* of patients	c/i SCI	Ejaculation in c/i SCI patients	Rhythmic forceful/ dribbling
Guttman, 1971/ UK	28/18–42	Frankel/no	nt	unk	134	102/32	53/25	unk
Piera, 1973/ France	unk	unk/no data	T10–S5	unk	74	56/18	10/10	unk
Grossiord, 1978/ France	unk/18–50	Frankel/yes	At each segment	unk/0.5–unk	30	30/0	21	RF = 16 Dr = 5
Chapelle, 1983/ France	unk/18–50	Upper and lower limit/yes	At each segment	unk/0.5–unk	20	20/0	9	unk
Chapelle, 1988/ France	unk/18–47	Upper and lower limit/yes	At each segment	unk/0.5–33	134	134/0	74	unk
Rawicki, 1991/ Australia	unk	Frankel/no	nt	unk	5	Unk	3 (nd)	unk
Chapelle, 1993/ France	unk/25–39	Upper and lower limit/yes	At each segment	unk/1–19	23	23/0	12	unk

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.

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 coïtus, 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 coïtus 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; $P < 0.0001$).

Comparison of ejaculation rates with PVS as a function of penile vibrator settings in patients with complete SCI

Optimal vibration parameters have been defined by Sonksen *et al.* (1994) as 2.5 mm amplitude and a frequency of 100 Hz. The ejaculation rate was 47.2% $n = 269$, CI 41.3–53.2) in studies using non-optimal vibration parameters and 44.3% ($n = 273$, CI 38.6–50.3, $P = 0.55$) in studies using optimal vibration parameters ($P = 0.55$).

Impact of the duration of SCI on ejaculation

According to grouped (Horne *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 coïtus 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 infra lesional ($P < 0.0001$). Masturbation

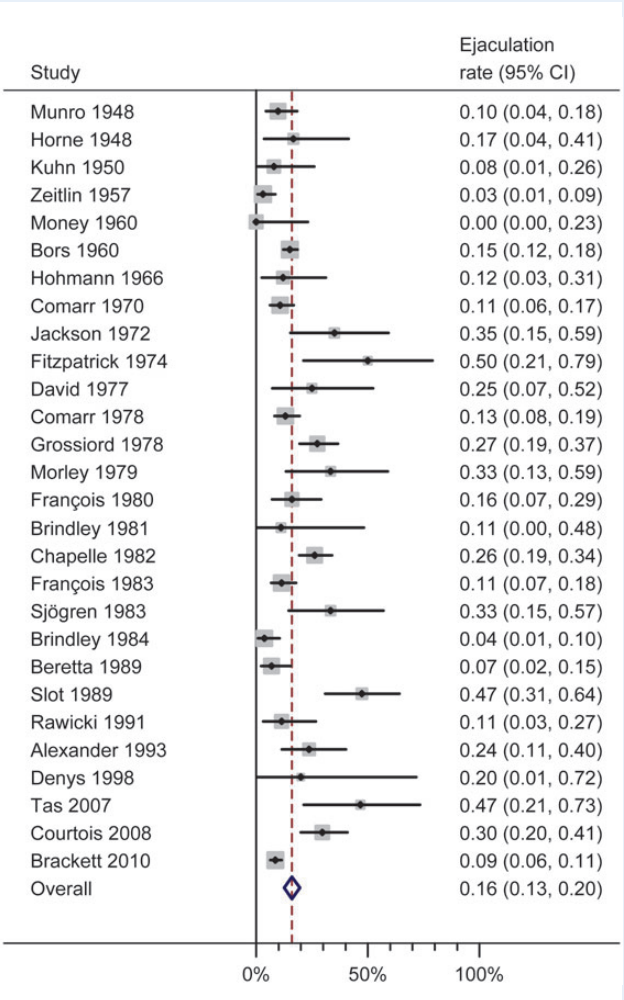

Figure 6 Ejaculation rate in patients with complete or incomplete SCI in response to masturbation or coitus, without the aid of medications or devices. Grey boxes represent the weight of individual studies and the dashed line represents overall pooled ejaculation rate using a random effect model.

following i.t. prostigmine or s.c. physostigmine in the case of failure of masturbation or coïtus 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 infra lesional ($P < 0.0001$). Masturbation following i.t. prostigmine or s.c. physostigmine in the case of PVS failure was used in one study (Piera, 1973). In this subset of patients the ejaculation rate was 0% ($n = 16$, CI 0–22.7) when the lesions extended from T12 to S5 and 81.2% ($n = 11$, CI 51.2–96) when the T12–S5 segments were infra lesional ($P < 0.0001$).

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

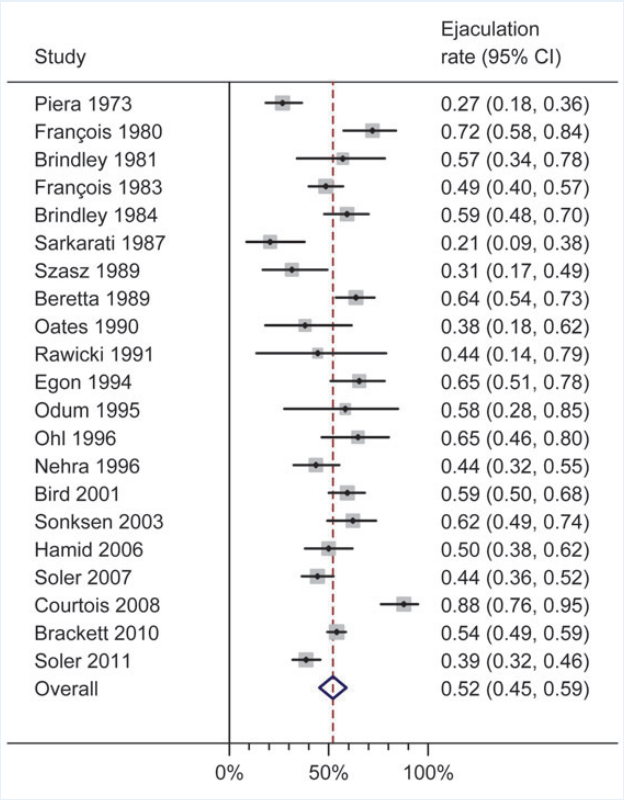

Figure 7 The ejaculation rate in patients with complete or incomplete SCI elicited by PVS. Grey boxes represent the weight of individual studies and the dashed line represents overall pooled ejaculation rate using a random effect model. PVS, penile vibratory stimulation.

T12–L2 segments and 90% (n = 30, CI 73.6–97.3) when the T12–L2 segments were infra lesional ($P < 0.0001$). Masturbation following i.t. prostigmine or s.c. physostigmine was used in four studies after failure of masturbation or coïtus 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 infra lesional ($P < 0.0001$).

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 infra lesional ($P = 0.006$). After failure of masturbation or coïtus 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 infra lesional ($P = 0.001$).

Characterization of ejaculation

The data presented in this review provide additional information about the characterization of ejaculation occurring during PVS or during

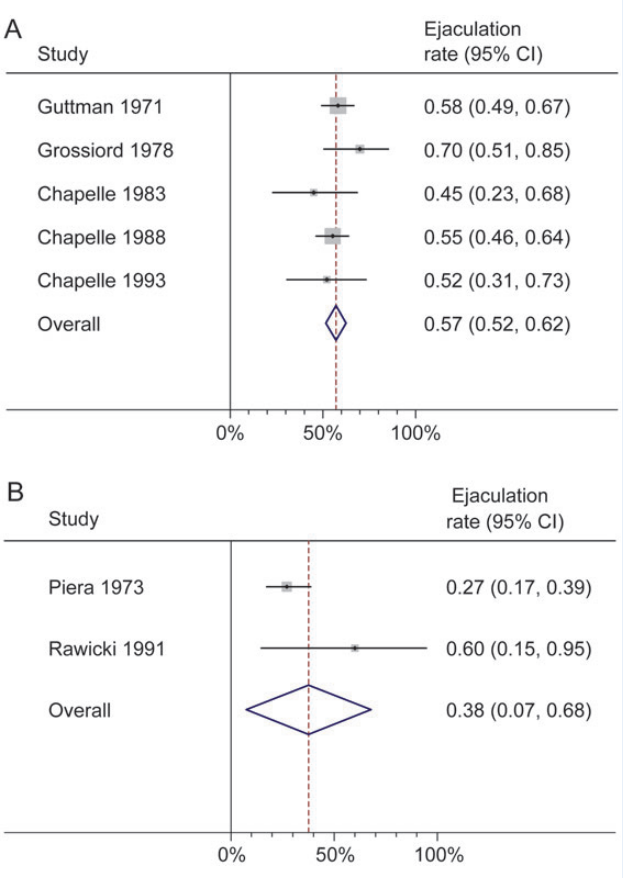

Figure 8 (**a**) The ejaculation rate in patients with complete or incomplete SCI during masturbation following intrathecal prostigmine or subcutaneous physostigmine after ejaculation failure of masturbation or coitus, without the aid of medications or devices. Grey boxes represent the weight of individual 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 intratechal 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.

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 coïtus without the aid of medications or devices in 5 studies (Zeitlin *et al.*, 1957; Comarr, 1970; David *et al.*, 1977; Brindley, 1981; Alexander *et al.*, 1993) and was self-reported to be rhythmic forceful by 20 patients and dribbling by 17. Ejaculation was elicited by PVS in 4 studies (Francois *et al.*, 1980; Brindley, 1981; Beretta *et al.*, 1989; Oates, 1990) and was documented by an investigator to be rhythmic forceful in 109 patients and dribbling in 12. Ejaculation occurred during masturbation following i.t. prostigmine in 1 study (Grossiord *et al.*, 1978) and was documented by an investigator to be rhythmic forceful in 16 patients and dribbling in 5.

In response to PVS or masturbation following i.t. prostigmine or s.c. physostigmine, ejaculation was documented by an investigator as rhythmic forceful in 0% ($n = 5$, CI 0–48.9) of patients with complete lesion encompassing S2–S4 compared with 97.9% ($n = 48$, CI 88.1–100) of patients with a lesion located above S2 ($P < 0.0001$). Similarly, ejaculation was documented by an investigator as rhythmic forceful in 0% ($n = 4$, CI 0–54.6) of patients with an upper limit of complete lesion at or below T12 compared with 98.7% ($n = 74$, CI 92.1–100) of patients with an upper limit of complete lesion above T12 ($P < 0.0001$).

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 infra lesional. 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 coïtus 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 (Fig. 2). 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. 9a). 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 infra lesional 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 infra lesional (Fig. 9c).

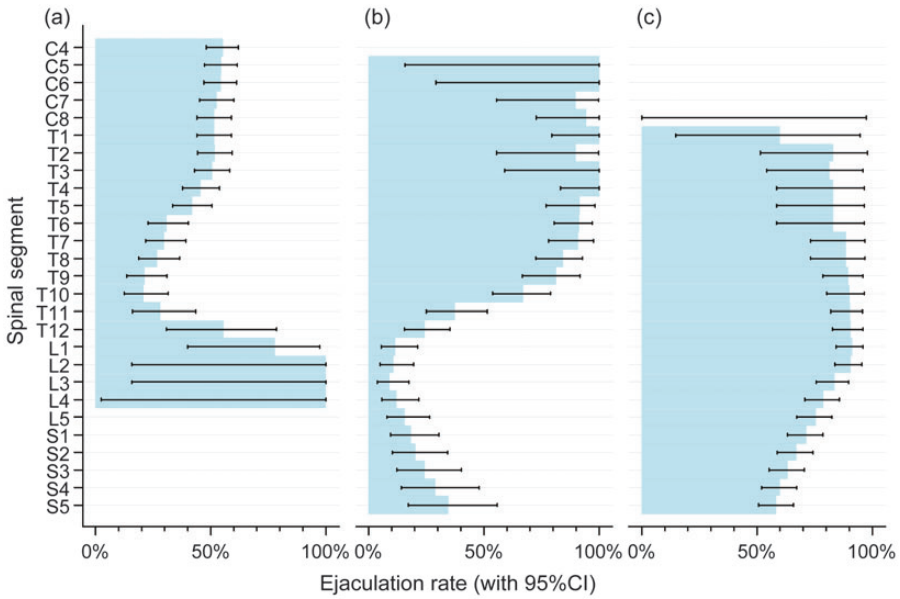

Figure 9 Ejaculation rates, with 95% confidence intervals, during masturbation following intrathecal prostigmine or subcutaneous physostigmine in patients with complete SCI according to the status of each spinal segment irrespective of the others: (**a**) supra lesional thus intact segment, (**b**) completely injured segment and (**c**) infra lesional segment.

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 coïtus 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 Ohl, 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 Sønksen *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 Sønksen'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 Ferticare^{R} 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

Table IV Ejaculation rates during masturbation after intrathecal prostigmine or subcutaneous physostigmine as a function of the status of the sympathetic centres (rows) and the lower limit of complete SCI (columns).

Number of segments completely injured between T12 and L2		Lower limit of SCI									Total	*P* value
		Above L3	L3	L4	L5	S1	S2	S3	S4	S5		
0 (Group 0)	Patients who ejaculated	80	0	0	0	0	0	0	0	0	80	<0.001
	Patients who did not ejaculate	8	1	1	0	2	0	1	0	0	13	
	Total nb of patients	88	1	1	0	2	0	1	0	0	93	
1 (Group 1)	Patients who ejaculated	18	0	0	0	0	0	2	0	1	21	<0.001
	Patients who did not ejaculate	2	0	1	2	1	1	2	0	2	11	
	Total nb of patients	20	0	1	2	1	1	4	0	3	32	
2 (Group 2)	Patients who ejaculated	1	0	0	0	1	0	0	0	2	4	1
	Patients who did not ejaculate	3	1	0	2	0	1	1	0	1	9	
	Total nb of patients	4	1	0	2	1	1	1	0	3	13	
3 (Group 3)	Patients who ejaculated	2	0	0	1	0	0	0	0	0	3	0.054
	Patients who did not ejaculate	7	5	4	5	7	6	5	5	14	58	
	Total nb of patients	9	5	4	6	7	6	5	5	14	61	
Together	Patients who ejaculated	101	0	0	1	1	0	2	0	3	108	<0.001
	Patients who did not ejaculate	20	7	6	9	10	8	9	5	17	91	
	Total nb of patients	121	7	6	10	11	8	11	5	20	199	

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 coïtus 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. prostigmine 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 prostigmine elicits or facilitates ejaculation when delivered it but not systemically (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 (Navaratnam 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 Krassioukov, 2006; Courtois *et al.*, 2008a; Ekland *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-Or *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). Intradetrusor 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 coïtus 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, coïtus 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 forceful 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 which allows intravaginal insemination at home for couples, without any further medical assistance. The possibility of conception, however, also depends on the quality of sperm which is often impaired in SCI patients. The overall rate of pregnancy following self-insemination ranges from 25 to 61% (Dahlberg *et al*., 1995; Nehra *et al*., 1996; Lochner-Ernst *et al*., 1997; Sonksen *et al*., 1997; Sonksen *et al*., 2012). If PVS fails or the self-insemination of semen retrieved by PVS is unsuccessful, sperm can be obtained by EEJ or more often by surgical retrieval, and then followed by assisted procreation techniques. After EEJ, intrauterine insemination, IVF or ICSI can be performed whereas after surgical sperm retrieval, IVF or ICSI is mandatory. Overall, EEJ or surgical sperm retrieval appears to be required for more than one-third of SCI patients in order for pregnancy to occur (Dahlberg *et al*., 1995; Brackett *et al*., 2010a). Low motility and viability of spermatozoa is a classic feature of sperm from SCI patients (Restelli *et al*., 2009). This is mostly due to the alteration in the seminal plasma (Brackett *et al*., 1997), the transportation/storage after sperm retrieval (Ohl *et al*., 1999) and the immune system changes which occur in SCI patients (Basu *et al*., 2002; Brackett *et al*., 2007a). Spermatozoa motility is higher when the SCI is incomplete and if it is located above the spinal ejaculation centres (Chapelle *et al*., 1993; Odum *et al*., 1995; Rutkowski *et al*., 1995; Sonksen *et al*., 1996). The retrieval method also influences semen quality, which is poorer when collected by EEJ compared with PVS, whereas the duration of SCI does not seem to exert an influence (Sonksen *et al*., 1996; Le Chapelain *et al*., 1998; Kafetsoulis *et al*., 2006; Iremashvili *et al*., 2010). Consideration of the quality of sperm in SCI patients is beyond the scope of the present review.

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 infra lesional. 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 infra lesional, 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 infra lesional 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 coïtus 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 infra lesional (data not shown). These data confirm the necessity for the T12–L2 segments to be infra lesional 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 infra lesional. However, this difference was less obvious than when comparing the complete lesion with infra lesional location of the T12–L2 segments. Conversely, the ejaculation rate during masturbation or coïtus without the aid of medications or devices was higher in the case of lesions of the S2–S4 segments than when these segments were infra lesional (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

patient. Injury of the S2–S4 segments usually induces more urine leaks because of urinary sphincter hypotonia or atonia. Urine leaks and bulbo urethral glands secretions occurring during sexual stimulation can be confounded with semen by patients (Zeitlin *et al.*, 1957). The results of the present review showed that ejaculation was not rhythmic forceful in any of the five patients with complete injury of the S2–S4 segments. In the four patients with an upper limit of complete SCI at the level of T12 or below, ejaculation was dribbling. All of these four patients had a complete SCI encompassing the S2–S4 segments. This strongly supports and confirms the crucial role of Onuf's nucleus located in these segments in the control of the expulsion phase.

Thus, the present data confirm the key role of (i) the T12–L2 segments in which the sympathetic centres which control emission are located and (ii) the S2–S4 segments in which the parasympathetic and somatic centres are located and command the emission and expulsion phases of ejaculation, respectively. If the T12–L2 segments are supra 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 highlighted 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 somatic reflexes 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 4 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 sacrolumbar 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 bulbospongiosus 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.

Data available from patients with complete SCI of the sympathetic centres (T12–L2; Grossiord *et al.*, 1978; Chapelle *et al.*, 1983a, 1988, 1993) allowed us to assess the impact of caudal extension of the injury below L2, at the level of the putative SGE (L3–L5). Among the patients with an upper limit of lesion above L3, ejaculation rate dropped sharply if the lower limit of the lesion was at L3 or below, compared with patients with an SCI lower limit above L3 (Table IV). This finding could be explained by the greater severity of the lesions affecting the T12–L2 segments when the lesion extends as far as L3 and below. This was, however, ruled out by statistical analyses controlling for lesions of the sympathetic centres. Ejaculation rates were further analysed in patient subgroups with the same number (between 0 and 3) of completely injured segments from T12 to L2. When the lower limit of the lesion was at the level of L3 or below, there was disruption of the intraspinal circuitry between the sympathetic and the parasympathetic and somatic centres whereas, when the lower limit was at L1 or above, there was no such disruption (Fig. 2; Brindley, 1981; Reitz *et al.*, 2002; Ertekin *et al.*, 2007). A complete injury at L2 similarly disrupts connections between sympathetic, parasympathetic and somatic centres even if the T12 and L1 segments are intact and could therefore explain the lower ejaculation rates observed in patients with lesions extending to L3 and below. The results of this review did not provide any support for this hypothesis: among patients with complete lesions at L2, those with a lower limit at L3 or below still had lower ejaculation rates (even if not statistically significant) than patients with a lower limit at L2 (data not shown).

In addition, the ejaculation rate was not lower in the case of lesions of the sacral segments (6/55) compared with when the sacral segments were infra-lesional (1/23). This further suggests a central role of the L3 to L5 segments in the observed drop in ejaculation rates when the lower limit of complete lesions is below L2. All together, these results suggest a key role of the L3–L5 segments in ejaculation, aside from the already described spinal autonomic and somatic ejaculation centres. In other words, these results support the hypothesis that lesions of the L3–L5 segments do not only disrupt the intraspinal circuitry, but also destroy the SGE thereby preventing coordinated activity of autonomic and somatic centres. Although no definitive evidence for the existence of an SGE in man can be provided, among publications about ejaculation and especially the 45 studies reviewed, no data against the existence of an SGE in man was found. Available clinical data are suggestive of the location of the SGE between the L3 and L5 segments.

Seven patients with complete SCI and absent spinal reflexes of the L3 to L5 segments could still ejaculate following i.t. prostigmine or s.c. physostigmine (Grossiord *et al.*, 1978; Chapelle *et al.*, 1988). These data are not necessarily in contradiction with the existence of an SGE in humans. The neurons which constitute the SGE in rats are interneurons. Lesions at a given level of the spine can lead to different types of involvement of the peripheral nervous system, i.e. rootlets, spinal roots and spinal nerves and/or the central nervous system, i.e. spinal cord may be affected. Complete spinal cord transection is rare even in the case of complete SCI (Kakulas, 1984). Aside from a lesion which spares the SGE, the rootlets, spinal roots and/or spinal nerves of L3, L4 and L5 can be injured. If the clinical examination shows that the L3, L4 and L5 spinal reflexes are abolished, it is likely that there is complete injury of these spinal segments. However, data provided by clinical examinations do not absolutely correlate with anatomical data (Grossiord *et al.*, 1978). The SGE, which coordinates smooth and striated muscle contractions leading to semen expulsion might have been

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. prostigmine or s.c. physostigmine. 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.

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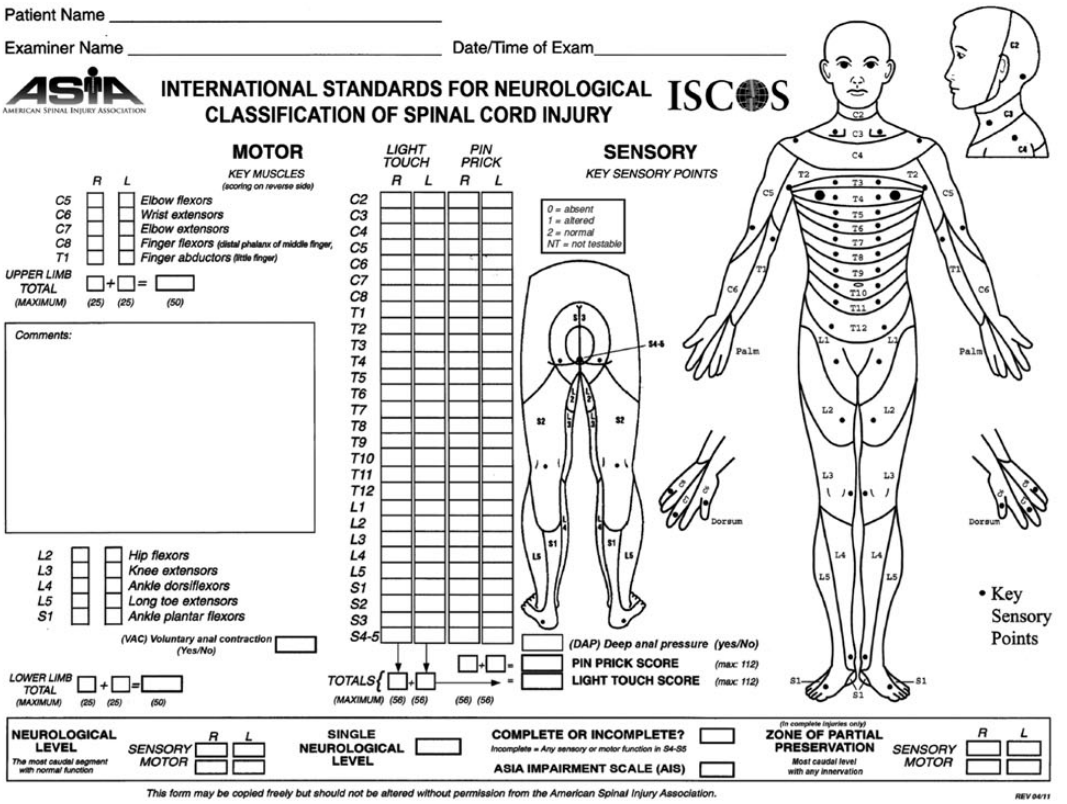
Appendix

American Spinal Injury Association: International Standards for Neurological Classification of Spinal Cord Injury, revised 2011; Atlanta, GA. Reprinted 2011.



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 moderate 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 peson.

5* = (normal) active movement, full ROM against gravity and sufficient resistance to be considered normal if identified inhibiting factors (i.e. pain, disuse) were not present.

NT = not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of >50% of the range of motion).

ASIA Impairment (AIS) Scale

☐ **A = Complete.** No sensory or motor function is 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 anal 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 (NLI) have a muscle grade less than 3 (Grades 0-2).

☐ **D = Motor Incomplete.** Motor function is preserved below the neurological level**, and at least half (half or more) of key muscle functions below the NLI have a muscle grade ≥ 3.

☐ **E = Normal.** If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient had prior 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 status, they must have either (1) voluntary anal sphincter contraction or (2) sacral sensory sparing with sparing of motor function more than three levels below the motor level for that side of the body. The Standards at this time allows even non-key muscle function more than 3 levels below the motor level to be used in determining motor incomplete status (AIS B versus C).

NOTE: When assessing the extent of motor sparing below the level for distinguishing between AIS B and C, the ***motor level*** on each side is used; whereas to differentiate between AIS C and D (based on proportion of key muscle functions with strength grade 3 or greater) the ***single neurological level*** is used.

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.
   Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level, if testable motor function above that level is also normal.
3. Determine the single neurological level.
   This 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 steps 1 and 2.
4. Determine whether the injury is Complete or Incomplete. (i.e. absence or presence of sacral sparing)
   If voluntary anal contraction = **No** *AND all S4-5 sensory scores =* **0** *AND deep anal pressure =* **No,** *then injury is COMPLETE. Otherwise, injury is incomplete.*
5. Determine ASIA Impairment Scale (AIS) Grade:

Is injury Complete? If **YES,** AIS=A and can record ZPP (lowest dermatome or myotome on each side with some preservation)

NO ↓

Is injury motor Incomplete? If **NO**, AIS=B (Yes=voluntary anal contraction OR motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)

YES ↓

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

NO ↓ AIS=C

YES ↓ AIS=D

If sensation and motor function is 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 at initial testing no deficits are found, the individual is neurologically intact; the ASIA Impairment Scale does not apply.