Pure alexia - some thoughts and a few experiments

Starrfelt, Randi

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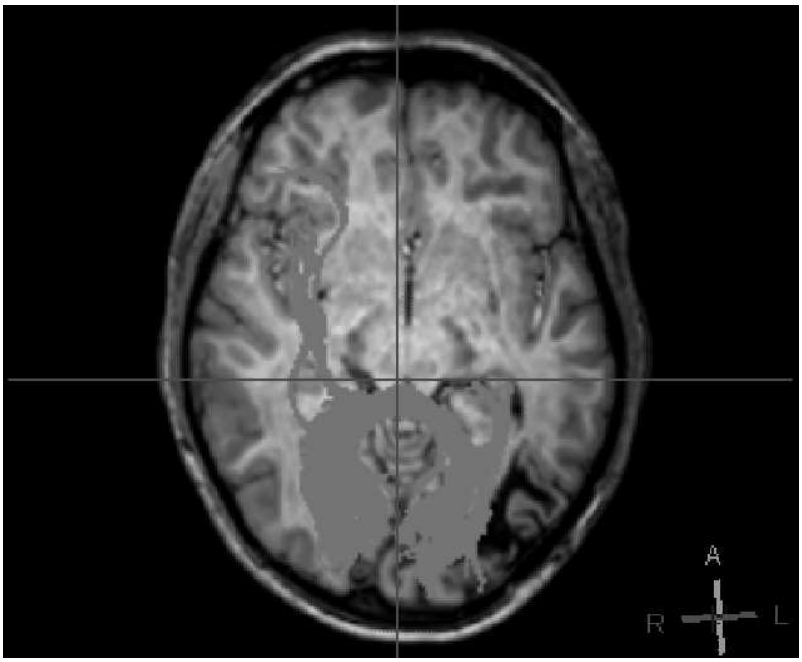

Pure alexia

- some thoughts and a few experiments

Doctoral Dissertation in Psychology

Randi Starrfelt

Department of Psychology
University of Copenhagen

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The relation of the sensation to the stimulus and the time taken up by mental processes are the two subjects in which the best results have been reached by experimental psychology. These results are important enough to prove those to be wrong who with Kant hold that psychology can never become an exact science.

From "The time it takes to see and name objects."
James McKeen Cattell (1886)

As an academic, I am not very different from a pure alexic: I write a lot better than I read.
Fakutsi

The truth is rarely pure and never simple.
Oscar Wilde

This dissertation is based on the following published articles (listed in order of appearance in the introductory text):

1. **Starrfelt, R.** & Behrmann, M. (2011). Number reading in pure alexia - a review. *Neuropsychologia, 43;* 2283-2298.

2. **Starrfelt, R.**, Lindegaard, M., & Bundesen, C. (2015). Confusing confusability: On the problems of using psychophysical measures of letter confusability in neuropsychological research. *Cognitive Neuropsychology*, *32*, 314-320.

3. **Starrfelt, R.,** Nielsen, S., Habekost, T., & Andersen, T.S. (2013). How low can you go?: Spatial frequency sensitivity in pure alexia. *Brain and Language, 126;* 188-192.

4. **Starrfelt, R.**, Gerlach, C., Habekost, T., & Leff, A.P. (2013). Word superiority in pure alexia. *Behavioral Neurology, 26;* 167-169. *

5. **Starrfelt, R.,** Petersen, A., & Vangkilde, S.A. (2013). Don't words come easy? A psychophysical exploration of word superiority. *Frontiers in Human Neuroscience , 7; 519.*

6. Habekost, T., Petersen, A., Behrmann, M., & **Starrfelt, R.** (2014). From word superiority to word inferiority. Visual processing of letters and words in pure alexia. *Cognitive Neuropsychology, 31;* 413-436.

7. Sand, K., Habekost, T., Petersen, A., & **Starrfelt, R.** (2016) The word superiority effect in central and peripheral vision. *Visual Cognition, 24;* 293-303.

8. Petersen, A., Vangkilde, S., Fabricius, C., Iversen, H. K., Delfi, T., **& Starrfelt, R.** (2016). Visual attention in posterior stroke and relations to alexia. *Neuropsychologia, 92*, 79-89.

9. **Starrfelt, R.** & Shallice, T. (2014). What's in a name?: The characterization of pure alexia. *Cognitive Neuropsychology, 31;* 367-377.

* The data, but not the main analysis presented in this paper were included as part of the author's PhD.-thesis

Preface

This dissertation presents a collection of studies concerned with pure alexia and visual word recognition conducted by the author in collaboration with colleagues and students both in Denmark and abroad. The research was supported by a University of Copenhagen Centre of Excellence grant to the Center for Visual Cognition, a Sapere Aude grant from the Independent Research Fund Denmark, Nexø Neuroscience, and the Friends of Fakutsi Foundation.

I would like to thank my co-authors, in particular my international collaborators: *Marlene Behrmann* for being an enthusiastic collaborator and inviting me to visit her lab and testing her patients; *Alex Leff* for all that, and a fruitful and long lasting collaboration on reading disorders; *Tim Shallice*, for agreeing to organize the pure alexia symposium with me, for suggesting a special issue on the topic, and for inspiring discussions during this work. In Copenhagen, I thank *Claus Bundesen* for supporting me throughout my academic career, and for always being willing to discuss theoretical aspects and experimental work; *Thomas Habekost*, for almost fifteen years of collaboration on the combination of psychophysics and the neuropsychology of reading; *Anders Petersen & Signe Vangkilde,* for stepping up when the TVA-analysis methods became too much to handle for a poor neuropsychologist, and for always being interested in my research questions; *Tobias Andersen & Simon Nielsen*, for explaining the difficulties in measuring spatial frequency sensitivity, and for helping me do it anyway; *Helle Iversen and Tzvetelina Delfi* for making it possible to recruit and scan patients at Glostrup hospital. Finally, students *Charlotte Fabricius* and *Katrine Sand* for doing all of the groundwork and much of the academic work in studies 7 and 8, and research assistant *Martin Lindegaard* for keeping all the patient data in order and contributing to study 3.

Last but always most: *Christian Gerlach* for all the long nerdy nights of neuroscience, and all the days and nights in between. And to *Lucca* for being Lucca.

Contents

1. Outline

This dissertation is concerned with the syndrome pure alexia, and how it may be characterized and understood. The selective impairment of reading in the context of intact writing and language has long intrigued both cognitive and clinical researchers. There is, however, no consensus about the cognitive (or cerebral) cause of the syndrome: After 40 years of research within cognitive neuropsychology, the core deficit in pure alexia is still elusive. This dissertation contains nine original articles. These address different hypotheses about the core cognitive deficit(s) in pure alexia, and how we may measure and understand this impairment. The conclusion of the dissertation is that pure alexia – although being a relatively simple syndrome – has been ill defined in the literature. This lack of stringency may have contributed to the relatively little progress made in the understanding of the pure alexia over the last two decades. Finally, two central questions in pure alexia research are discussed, and a novel hypothesis about the cognitive cause of pure alexia suggested.

2. Pure alexia[1]

Patients with pure alexia can write, but they can't read. They can walk, talk, remember, and find their way around, and they rarely complain about problems with recognizing other visual objects, faces, or places. But when it comes to deciphering written words or text, they find themselves unable to read with the ease and fluency they did before their brain injury. This disorder has intrigued researchers for well over a century, but although many facets of the patients' reading behaviour and lesion anatomy have been investigated and described, the mystery of how the ability to read can suffer while the ability to write remains intact is still not resolved.

Pure alexia is a selective disorder of reading caused by damage to posterior structures in the dominant hemisphere. The disorder is selective in the sense that other language functions, including writing, are intact. However, subtle visual deficits have been reported to accompany pure alexia in many patients (e.g., Mycroft, Behrmann, & Kay, 2009; Starrfelt,

[1] Parts of this introduction are based on Chapter 3. Pure Alexia, in the book *Alexia* (Leff & Starrfelt, 2014), written by the author (author declaration included in Faculty material).

Habekost, & Gerlach, 2010; Starrfelt, Habekost, & Leff, 2009). Many different labels have been used for this disorder, e.g., *alexia without agraphia*, *pure alexia, verbal alexia, global alexia, letter-by-letter (LBL) reading*, and *spelling dyslexia.* Some labels indicate degree of severity (global alexic patients are totally unable to read even single letters) while other focus on the compensating strategies utilised by the patients (LBL-reading and spelling dyslexia).

Pure alexia is most commonly seen as a consequence of stroke (infarcts or haemorrhages) in the territory of the posterior cerebral artery in the left hemisphere, and such patients are also most common in the neuropsychological literature, but pure alexia has also been reported following a variety of other brain diseases (Adair, Cooke, & Jankovic, 2007; Erdem & Kansu, 1995; Mao-Draayer & Panitch, 2004).

A core symptom of pure alexia is an effect of word length on reading time for single words, which has typically be interpreted as reflecting serial processing of the letters in words (Barton, Hanif, Eklinder Björnström, & Hills, 2014; Bormann, Wolfer, Hachmann, Neubauer, & Konieczny, 2015), contrasted with the parallel processing of letters seen in normal reading (Adelman, Marquis, & Sabatos-DeVito, 2010; McClelland & Rumelhart, 1981). Since the 1980's, many studies within cognitive neuropsychology have focused on understanding and explaining the word length effect (WLE). These cognitive studies try to identify the cause of the compensating mechanism, letter-by-letter reading, rather than the cognitive or cerebral basis of a particular syndrome like pure alexia. This has resulted in a somewhat chaotic literature on pure alexia/LBL-reading. While most patients with pure alexia do show a word length effect in reading, patients with other types of alexia, and with other, associated deficits may also use a spelling strategy in reading (Cumming, Patterson, Verfaellie, & Graham, 2006; Woollams, Hoffman, Roberts, Lambon Ralph, & Patterson, 2014). Thus, many patients with agraphia or major cognitive or visual deficits have been included in the study of LBL-reading. This maybe be unproblematic from a cognitive neuropsychological perspective (although see Shallice, 2014), but it is important when one tries to understand pure alexia to keep the syndrome (defined by the absence of aphasia and agraphia) and the reading strategy (LBL-reading) apart.

For the purposes of this dissertation, I will define the core concepts in the following way: **Pure alexia** refers to reading impairment observed in patients who show a deficit in single word reading that is evident in reaction times when reading both horizontally and vertically presented words. The patients usually show a significant word length effect in

single word reading, where RTs increase monotonically for each additional letter in a word. This effect is commonly in the range of a few hundred milliseconds to a few seconds per letter. Patients may, however, also be totally unable to read, an impairment sometimes referred to as **global alexia**. Patients with pure (and global) alexia do not have other aphasic deficits (although mild slowness in picture naming may be present), and, importantly, do not have agraphia, but perform normally on writing tests. Patients may have trouble writing whole sentences or text, however, as they are impaired in reading back what they have just written. **LBL-reading** is a strategy that patients use for different reasons cognitively and anatomically. It is either evident because the patients spell words overtly, or it can be inferred from a significant effect of word length on reading latency. Patients with LBL-reading may make reading errors like regularisation errors (sometimes called LBL-surface alexia (e.g., Friedman & Hadley, 1992), or have other deficits in language and/or cognition (Cumming et al., 2006; Woollams et al., 2014). The concept LBL-reading is in many ways broader than pure alexia, and also less specific. Some patients with milder forms of pure alexia read too quickly to really be using a LBL strategy, but still show word length effects far outside the normal range.

Two main questions about pure alexia receive continuing attention, but have to date not been satisfactorily answered. These are: 1) What is the core deficit?, and 2) How selective (or general) is this deficit? The two questions are clearly related, and included in this dissertation are papers addressing both. This introduction will serve to present the included articles in context, and seeks to provide an integrated overview of how they may contribute towards a better understanding of pure alexia from a cognitive neuropsychological perspective. This dissertation is mainly concerned with behavioural aspects of pure alexia, and does not discuss the cerebral substrate to any large degree (for an anatomical discussion see e.g., Leff & Starrfelt, 2014).

3. How selective is the deficit in pure alexia?

A main question in pure alexia research has been whether this syndrome affects reading only, or if (visual) processing of other categories of stimuli is also affected. Traditionally, the main question has been if processing of objects or drawings are impaired in this patient group, and much previous research has addressed this possibility (e.g., Behrmann, Nelson & Sekuler, 1998; Sekuler & Behrmann, 1996; Starrfelt, Habekost, & Gerlach, 2010;

reviews in Farah, 1990; 2004). These works all concluded that pure alexia is "not pure", as processing of other types of visual stimuli are also affected. In contrast, some studies indicate that pure alexia may be selective to letters and words only (Cohen, Dehaene, McCormick, Durant, & Zanker, 2016; Gaillard et al., 2006), and does not necessarily affect object recognition. The most similar stimulus type to compare letters and words to, however, are probably not objects but digits and numbers.

Letters and digits are only different by cultural convention. To someone not familiar with these symbols, *2* could easily be a letter, and *B* a number, so it is only through learning that these symbols are attributed to different categories. If pure alexia is so selective that it affects recognition of letters but not numbers, it would be difficult to ascribe it to a general visual deficit. Rather, a selective deficit in reading alphabetic characters would be the preferred explanation for the syndrome. This would also have consequences for theories of the cognitive and cerebral organization of the reading system; if reading of alphabetic characters can be affected selectively following injury to the brain, it follows that there must be a region (or regions) in the brain dedicated exclusively to processing these symbols.

3.1. Number reading in pure alexia

Starrfelt & Behrmann (2011)

It is commonly stated that number reading can be intact in pure alexia, and this finding is typically attributed to Dejerine (1892). It has, however, become clear that even this original case did not show a classical dissociation between letter and number reading, as Dejerine's patient, Monsieur C, was also impaired in number reading, just to a smaller degree that with letters (Bub, Arguin, & Lecours, 1993).

Much of the author's previous work has been concerned with the possible dissociation between reading of letters and digits in (pure) alexic patients (Starrfelt, 2007; Starrfelt et al., 2009; 2010). In the studies of patients with pure alexia, we failed to find a dissociation between reading and visual processing of letters and numbers. Rather, the patients were impaired with both symbol types in a similar way and to quite a similar degree.

A problem with drawing conclusions on this basis, however, is that this pattern constitutes an association between deficits, which has traditionally not been considered a strong form of evidence in cognitive neuropsychology. While we could potentially have gone

on recruiting pure alexic patients and testing their number reading abilities in search for a dissociation, another way of addressing the problem seemed more promising: Reviewing the literature in search of a clear dissociation between letter and number reading. In principle (in cognitive neuropsychology), a single patient showing a clear dissociation should be enough to conclude that the identification of letters and numbers can indeed be affected selectively, although more patients would provide stronger evidence.

In a comprehensive review of published studies of pure alexia, we (Starrfelt & Behrmann, 2011) selected all papers reporting anything at all on how the patients read Arabic numerals. Of the 223 papers reviewed, of which Dejerine's (1892) original patient study was one, 76 papers mentioned number reading performance in a total of 90 patients. In 46 of these patients, number reading was reported to be impaired at the same level as letter identification. For 28 of the 44 remaining patients, no data were presented to make an evaluation of the dissociation possible. These studies did not have a comparison between stimulus types as their main objective, and thus typically only stated in the patient descriptions that number reading was "intact", "flawless" or "unimpaired". For a further 5/44 patients, the tasks with letters and digits were too different for any meaningful comparison to be made between them. Notably, the dissociation in all these 33 cases was in the direction number performance > letter performance. Although striking at first glance, it is of course less surprising when one considers that all the patients were selected because they had problems with reading letters and words (i.e., pure alexia).

For the 11 patients for whom both letter and number reading was sufficiently sensitively tested, we needed a way of classifying the evidence. While early cognitive neuropsychologists were satisfied with using accuracy as an outcome measure, and commonly neither compared patients' performance to normal controls nor used any form of statistics, we found it appropriate to review the data using more modern standards for showing dissociations.

3.1.1. A methodological consideration

Shallice (1988) described three forms of dissociations, constituting increasing evidence for selectivity or separability: (i) A *trend dissociation*, where a patient's score on task I is markedly lower than on task II, but where performance is not compared to a control

group; (ii) a *strong dissociation*, where "neither task is performed at a normal level, but task I is performed very much better than task II" (p. 228). In this case, performance is commonly compared to a normal control group, but a patient's performance on tasks where normal controls would be expected to perform at ceiling may also constitute evidence for a strong dissociation (i.e. in the absence of directly comparing the patient to a control, one assumes perfect or near-perfect performance for normal individuals); and (iii) *a classical dissociation*, where - relative to normal controls - performance on task I is impaired while performance on task II is within normal limits. While trend dissociations are taken as a weak form of evidence, both strong and classical dissociations have been interpreted as suggestive of specialized functions or modularity. Aiming to make the matter more about formal comparisons, and less about assuming normal performance, John Crawford and colleagues have suggested more refined (and operational) criteria specifying statistical demands for dissociations (e.g., Crawford & Garthwaite, 2005; Crawford, Garthwaite, & Gray, 2003). In brief, this approach demands that, in order to conclude that there is a classical dissociation, the patient's scores should differ significantly from the control group on one of two tasks, while performance should be within the normal range on the other task, and - importantly - the difference between the patient's standardized scores in the two tasks should be significant. For the less stringent strong dissociation, there should be a significant difference between the patient's standardized scores on the two tasks in question, while both scores may differ significantly from the mean of the control group.

3.1.2. Impaired letters but not numbers?

Returning to the 11 patients where both letter and number reading was assessed, and sufficient details reported, it was again noticeable that all patients performed better with numbers than with letters. To test whether any of these results constituted a real dissociation, we used the concepts derived from Shallice (1988) and Crawford et al.'s methods for analysing single case data, to determine the presence of a dissociation. Doing this, we found that six of these patients showed a *trend dissociation*, with better performance with numbers than letters without reference to controls. The tasks used were generally not very sensitive

and most comparisons were based on accuracy scores, which, while useful, might not be sufficiently discriminatory.

Very few studies of pure alexic patients have explicitly aimed to compare performance with letters and with digits, and few make formal comparisons of patients' performance with the two types of symbols. We identified four studies (reporting five patients) that did make such a comparison and report a difference between patients' performance with letters and digits, i.e., indicating a strong dissociation. Two of these studies compare patient performance to normal controls (Perri, Bartolomeo, & Silveri, 1996; Starrfelt et al., 2010), while one includes a group of patient controls without pure alexia (Ingles & Eskes, 2008). The fourth study (Cohen & Dehaene, 1995) may only meet the formal criteria for a trend dissociation, as they do not compare the patients' performance to controls. We chose to include the study as a potential strong dissociation, however, as it had as its stated goal the investigation of number processing skills in pure alexia, controls would be expected to perform at ceiling in their tests, and the patients' performance with letters and digits in the same task was statistically compared. In sum, these four studies did show better performance with numbers than letters, but none of the papers provided evidence of a classical dissociation.

In our review, we then went a step further, and subjected available data (from Starrfelt et al., 2009; 2010) to Crawford's test for a dissociation. In short, what we found was that even the patients showing the largest difference between performance with letters and numbers did not show a statistically significant dissociation (neither classical nor strong). To sum up, Starrfelt & Behrmann (2011) found no evidence in the literature supporting a classical dissociation between number and letter reading, i.e., there was no pure alexic patient on record with convincingly demonstrated intact number reading skills in the context of impaired letter recognition. It is curious, though, that all the patients show better performance with numbers than letters, even if a clear dissociation is not present.

3.1.3. Are numbers just easier to read?

As Shallice (1988) made clear, the preferred explanation for a dissociation is that one task is just easier than the other. This is why comparison with normal controls is so important. An likely explanation, then, for the better performance with numbers than letters

seen in the patients, is that identifying numbers is just easier than reading letters. We (Starrfelt & Behrmann, 2011) put this hypothesis to a test, by investigating the identification of single letters and digits in a sample of young, normal observers. Using a psychophysical test-paradigm with very brief, masked exposure, we were able to measure the visual processing component of number and letter encoding. A bit to our surprise, what we found that these subjects could identify briefly presented digits better than letters even when stimulus sets were equated with regards to visual complexity and number of stimuli. This indicates that digits are significantly easier to identify than letters for normal subjects when the perceptual information about the stimuli is limited. This further suggests that the tendency towards better performance with digits than letters in pure alexic patients might reflect an amplification of a normal difference in symbol processing (see Schubert, 2017 for a discussion of possible reasons for this difference). Supporting this notion, a recent comprehensive case study of a patient with (pure) alexia demonstrated quite convincingly that the deficits in reading letters and numbers arise at the same level of processing (McCloskey & Schubert, 2014).

The observation that pure alexic patients have deficits in digit as well as letter identification, and are also commonly impaired in recognizing objects, suggested that a general deficit in visual processing affects the processing of at least these forms of visual stimuli, and perhaps all visual stimuli. If this is indeed the case, it is likely that this deficit affects a mechanism relatively early in visual processing. A central hypothesis about this deficit is presented in the next chapter.

3.2. Letter confusability and degraded visual input

While quite a few explanations for pure alexia have been suggested over the years, no consensus has yet been reached on most of the main issues. Some have suggested that there are several types of pure alexia (Hanley & Kay, 1996; Rosazza, Appollonio, Isella, & Shallice, 2007), while others insist that a common explanation can be found (Behrmann, Plaut, & Nelson, 1998). In a 1995 paper, Behrmann & Shallice stated (somewhat resigned) that, “At present, the number of possible interpretations of the mechanism underlying letter-by-letter reading almost equals the number of patients who demonstrate the deficit” (Behrmann & Shallice, 1995 p. 410), and this still seems to be true.

3.2.1. Letter confusability in (pure) alexia

Starrfelt, Lindegaard, & Bundesen (2015)

Letter identification is impaired in the majority of pure alexic patients (Behrmann et al., 1998b) and a series of studies by Arguin, Fiset and colleagues (Arguin, Fiset, & Bub, 2002; Fiset, Arguin, Bub, Humphreys, & Riddoch, 2005; Fiset, Arguin, & McCabe, 2006; Fiset, Gosselin, Blais, & Arguin, 2006) indicated that *letter confusability* might be the important variable in determining the reading speed of LBL-readers / pure alexic patients. Letter confusability refers to the similarity between a given letter and all other letters in the alphabet, as determined by psychophysical studies in normal observers (e.g., Loomis, 1982; Mueller & Weidemann, 2012; Townsend, 1971).

In a study of seven LBL-readers (of which only one was documented to have pure alexia without agraphia or other major cognitive deficits), Fiset et al. (2005) found that when the summed letter confusability (a value created by adding the confusability values for each letter in the word) was matched across word lengths, the WLE "disappeared". In single letter naming, the patients showed no effect of letter confusability on RTs, although these RTs were still elevated compared to controls. When the confusability of letters in words was left uncontrolled (which means that the summed letter confusability for words increase with word length), the typical WLE was found in the LBL-patients. The normal controls showed no effect of letter confusability or word length when tested with the same material. This led Fiset et al. (2005) to suggest that letter-by-letter dyslexia (which they call it) should be renamed *letter confusability dyslexia.* Further experiments revealed that the effect of letter confusability on word reading latencies was only present in the patients when letters were presented simultaneously (i.e., the whole word was shown on one line). When letters that formed a word were flashed sequentially, one letter at a time, or letters were presented skewed, so that half the letters appeared one line below the others, there was no effect of confusability on RTs. This led to the conclusion that the effect of confusability in LBL-reading arises only when letters are processed in parallel.

In the literature, several studies began to control for this parameter although very loosely defined (e.g., Cushman & Johnson, 2011; Pflugshaupt et al., 2011), while few investigated the effect further. Or maybe the results were just not published? We first aimed to investigate the effect further, to see if we could replicate the effect of letter confusability on

RTs, and in what type of task (Starrfelt, Lindegaard, & Bundesen, unpublished data). While we did actually collect data to look more closely at the effect by comparing the confusability values calculated by Arguin et al. (2002) to more recent confusability measures for a specific font (Petersen & Andersen, 2012), it soon became clear that the definition of letter confusability, and the theoretical basis for the measures used to determine it, were too problematic for these data to be meaningful.

Starrfelt, Lindegaard, & Bundesen (2015) instead wrote a commentary, pointing out what these problems were. It is worth dwelling a little on the calculations and data behind the letter confusability measure used in studies of LBL-reading because at first glance, the effects of this variable on alexic reading seem so clear (Fiset et al., 2005; Fiset, Arguin, et al., 2006). Yet when we look at what the confusability measure actually reflects, it becomes quite unclear why it would be of any importance in word reading. The confusability value used in the studies of confusability effects in LBL-reading is an average score based on four older psychophysical studies of letter similarity (Gilmore, Hersh, Caramazza, & Griffin, 1979; Heijden, Malhas, & Roovaart, 1984; Loomis, 1982; Townsend, 1971). These studies all employed different methods (presentation mode (central/peripheral), fonts, and exposure durations) for creating so-called confusability matrices. A confusability-matrix is based on data from psychophysical experiments where stimulus exposure is carefully controlled, so that normal subjects identify letters correctly about half of the time, and thus half of the time they make errors - 'confusions'. A list of these confusions - the number of times a given letter is recognized as another specific letter in the alphabet - is then created. Arguin et al. (2002) did the following based on these matrices: First, they created a mean error score per letter for each study (i.e., calculated the number of times a given letter was reported to be any other letter of the alphabet), then they averaged these error scores across studies to create a single confusability score for each letter in the alphabet.

This may seem straightforward, but averaging over studies that have used different fonts, masking conditions, and even studies using either central or peripheral presentations, is not trivial. All these manipulations are known to affect perceivability of visual stimuli, but may do so differently, and indeed there are not very high correlations between the confusability measures used for calculating the average score used in the different studies by Fiset, Arguin et al. (see Starrfelt et al., 2015, Tables 1 and 2). It is also problematic to simply add up mean scores from single letter identifications tasks to characterize the 'confusability' of a word.

Although to our knowledge this has never been tested, it seems likely that misidentifications (confusions) of letters within words are different from those observed in single letter tasks. It is also puzzling that in single letter naming, Fiset et al. (2005) find no effect of letter-confusability on RTs in their LBL-patients (although RTs are elevated compared to normal subjects). It seems peculiar that confusability – a parameter derived from normal subjects' performance with *single* letters – should have no effect on single letter identification, while it does have an effect on word reading. Another aspect of Fiset et al.'s (2005) study that deserves mentioning is that although the WLE "disappears", the elevated reaction times remain: The patients have RTs that are very significantly out of the normal range, even when summed letter confusability is controlled.

In sum, although there are potentially interesting findings regarding letter confusability effects in LBL-reading, it is difficult to know what these effects reflect. Confusability is not a clear index of visual similarity between letters (at least not for more than a specific font given specific viewing conditions), and we do not know how confusability for single letters relates to the confusability of letters within words. Thus, Starrfelt et al. (2015) concluded that the effect should be further investigated, preferably by using more controlled material, but that it was premature to control for this variable in experimental studies (or clinical tests).

3.2.2. Is pure alexia due to reduced sensitivity to certain spatial frequencies?

Starrfelt, Nielsen, Habekost & Andersen (2013)

Based on their studies of letter confusability mentioned above, Fiset and colleagues (Fiset, Gosselin, et al., 2006; Tadros, Fiset, Gosselin, & Arguin, 2009) went on to suggest a quite concrete hypothesis about what kind of visual deficit that causes pure alexia (or really LBL-reading). While we have been critical to the letter confusability studies, the reported effects still need explanation, and the one offered by Fiset, Gosselin et al. (2006) was that pure alexic patients have a reduced sensitivity to certain spatial frequencies, which cause them to read letter-by-letter. By filtering out certain (medium range) spatial frequencies from word stimuli, they induced elevated RTs and a word length effect, as well as effects of letter confusability, in normal subjects. With such degraded stimuli, the mean RTs and WLEs of the

normal subjects were in the range seen in pure alexic patients/LBL-readers, and interestingly the mean RTs also varied considerably between subjects (like it does in patients). Based on this, Fiset, Gosselin et al. (2006) suggested that the main deficit in LBL-reading may be on the level of extracting medium spatial frequency information from visual (word) stimuli, and that serial processing – automatic or strategic - is necessary to extract the (higher) spatial frequencies for letter- and by that word identification.

Roberts et al (2013) provided some further support for this hypothesis. They tested eight alexic patients with left occipito-temporal lesions (for whom they do not report any writing tests) on a standard, paper-and-pencil contrast sensitivity test (The functional acuity contrast test: http://www.stereooptical.com/). This test uses simple, striped stimuli (Gabor patches) rather than filtered words. They found that, on average, these eight patients showed reduced sensitivity for medium to high spatial frequencies (6 – 18 cycles per degree (cpd)). This suggests that only sensitivity for the lowest (< 6 cpd) spatial frequencies are preserved in these patients, so that their residual reading abilities may either rely only on these low frequencies, or that effortful attention to single letters is necessary to extract medium or high frequencies for letter and word identification.

The spatial frequency hypothesis of pure alexia deserves praise for its simplicity, specificity, and clarity – and for being falsifiable: Pure alexia/LBL-reading is caused by reduced sensitivity to medium spatial frequencies in visual input. This deficit is general to all visual input, but as these particular spatial frequencies are less important for identifying other objects, it is not "a real nuisance for other classes of objects" (Fiset, Gosselin, et al., 2006, p. 1472). Thus, the hypothesis not only explains pure alexia / LBL-reading as a general visual deficit, but also why behaviourally it seems so selective. The hypothesis has received support from experiments with normal subjects (Fiset, Gosselin, et al., 2006; Tadros, Dupuis-Roy, Fiset, Arguin, & Gosselin, 2013), functional imaging (Woodhead, Wise, Sereno, & Leech, 2011), and importantly patients with (pure) alexia (Roberts et al., 2013).

In order to put this hypothesis to a stringent test, we (Starrfelt, Nielsen, Habekost, & Andersen, 2013) devised a sensitive psychophysical paradigm for testing contrast sensitivity for different spatial frequencies. Testing a patient with pure alexia, we found that she performed normally (compared to matched controls) across a large range of spatial frequencies s (1 – 16 cpd). This was the case in both a detection and a discrimination paradigm. We did not test our patient on filtered word stimuli, because the hypothesis holds

that patients have a general deficit in extracting the relevant frequencies, and our patient did not. Thus, this ”black swan” counters the hypothesis as it was originally suggested; reduced sensitivity to certain spatial frequencies cannot explain all cases of pure alexia, and thus fails as a general explanation for the syndrome. However, the spatial frequency hypothesis deserves further investigation and perhaps refinement, as it is still neither strongly supported nor entirely refuted. It stands as the most easily testable hypothesis of pure alexia to date, and for this it deserves both credit and the attention of future research.

Although it seems unlikely that pure alexia is reducible to a deficit in spatial frequency sensitivity, a common, low-level deficit causing pure alexia and the commonly associated perceptual deficits is not yet ruled out. It has also become increasingly clear that whatever the core deficit in pure alexia is, it has a more pronounced effect on word reading than on recognition of other visual stimuli (although recent work suggests that faces may be an exception, Behrmann & Plaut, 2014; Roberts et al., 2015; see Robotham & Starrfelt, 2017 for a critical discussion). Forcing a link between this general visual deficit and impaired word processing in pure alexia has proved difficult, but the line of studies presented next has made an attempt at this.

4. Lexical effects and word superiority

In some of our earlier studies, we showed that visual processing speed and apprehension span was reduced for both letters and digits in pure alexia (Starrfelt et al., 2009; 2010). On this basis, we suggested that “even slight reductions in the efficiency of letter recognition and discrimination will have a disproportional impact on reading, particularly when coupled with reduced visual apprehension span, and we suggest that this is the case in pure alexia. This does not imply a word specific deficit, but merely reflects that, for the purposes of fluent reading patients with pure alexia see *too little, too late*” (Starrfelt et al., 2009, p. 2889). The next question, then, was how this reduced processing capacity might affect processing of letters in words (i.e., word reading).

4.1. Word superiority in pure alexia

Starrfelt, Gerlach, Habekost, & Leff (2013)

Our first attempt to study this was only partly successful: Seeking to test whether the general reductions in visual apprehension span and processing speed for letters and numbers had an effect on word processing, we devised a *word superiority* experiment. Even though it is generally agreed that normal readers read words by processing their constituent letters, people are better at processing known words than single letters or meaningless letter strings. This effect is known as the *word superiority effect*, and was noted at least as early as the 1880s. James McKeen Cattell, who spent much of this time working on "The time taken up by cerebral operations"(Cattell, 1886b), noted that reading out the letters of a word, e.g., [silence], was faster than reading out the same letters when they did not make a word, e.g., [lensice]. Perhaps even more surprisingly, he also found that his subjects were faster at naming words than single letters (Cattell, 1886a). This *word superiority effect (WSE)* has received much attention in cognitive studies of visual word recognition and has come to denote not a difference in naming time, as Cattell originally observed, but in visual processing or encoding time: Normal readers are better at identifying letters embedded in words than in letter strings when stimulus presentation is degraded or brief (McClelland & Johnston, 1977; Reicher, 1969; Wheeler, 1970). The effect is commonly investigated in experiments where words or letter strings are presented very briefly and then masked. In the classic paradigm, the presentation of the stimulus (e.g., WORD) is followed by a forced choice between two letters (_ _ _ D or _ _ _ K) or two confusable words (WORD or WORK). In the free-report paradigm, subjects are merely asked to report all the letters they have seen in the correct order. This latter paradigm is more sensitive (normals make more errors, and chance level is very low), and has been suggested to be the most appropriate for testing alexic patients (Bowers, Bub, & Arquin, 1996).

There are a few case studies of the word-superiority effect in pure alexia, and these present contradicting findings: Some studies report a significant WSE (Bub, Black, & Howell, 1989; Reuter-Lorenz & Brunn, 1990), while others do not (Behrmann, Black, & Bub, 1990; Kay & Hanley, 1991; Starrfelt et al., 2010). However, these studies typically report single patients using specifically developed paradigms, and few patients have been investigated using the same methods making results hard to compare between studies.

Taking Bowers et al.'s (1996) advice on what paradigm was best suited for studying alexic patients, we designed a free-report paradigm to test the hypothesis that reductions in visual processing speed and apprehension span affected word reading in pure alexia (Starrfelt, Gerlach, Habekost, & Leff, 2013). We tested the same four patients for whom Starrfelt et al. (2009) reported reduced visual speed and span for both letters and digits. The results were as follows: As expected, patients reported fewer letters than controls from both words and nonwords. They were, however, significantly better at reporting letters from words than non-words, i.e., they showed a word superiority effect. More interestingly, we found that the size of their WSE differed markedly from each other. Three patients showed a WSE significantly *smaller* than controls (in spite of control subjects performing almost at ceiling in both conditions). The fourth patient, however, showed a WSE that was significantly larger than the other patients', and also non-significantly higher than that of the controls. There was no clear relation between the presence of or size of the word superiority effect and the patients' RTs in reading or the slope of their word length effect. What was evident, however, was a relationship between the size of the patients' visual field defect and their WSE. The patient with the best overall performance and the largest WSE had full visual fields (i.e. no visual field defect). It is curious though, that this patient was not the best reader when judged by RTs or WLE, and it is a bit of a mystery, why he should perform so well in the letter report task. In hindsight, it would have been interesting to know whether he would be able to explicitly report the *words*, not only their constituent letters, based on this brief presentation, or if he was perhaps dependent on explicit letter identification to read words (e.g., Warrington & Langdon, 1994).

The pure alexic patients included in this study show an effect of lexicality on the number of letters they can process / report, but several aspects of the results were more intriguing than enlightening. One curious aspect was that the performance of the controls was at ceiling level for words of seven letters, and almost as high for nonwords. That is, controls were able to report many more independent letters than suggested by their visual apprehension span (as measured in the peripheral visual field). This could be due to the central presentation, but also seemed to indicate an effect of top-down processing or fast phonological recoding even for nonwords.

4.2. A detour to experimental psychology – devising a new experiment

Starrfelt, Petersen, & Vangkilde (2013)

The word superiority effect has mostly been studied in normal readers, and it is indeed a curious phenomenon. Words are not considered to be processed as visual units, but rather as fast parallel processing of the individual letters, supported by top-down activation from partially matching words in visual long term memory. And yet, word processing is superior even to the processing of single letters, an effect sometimes referred to as the *word-letter* effect (Jordan & Patching, 1994). This, like the word – pseudoword superiority effect, has been interpreted as an effect of top down processes enhancing visual recognition of words. In typical experiments, this is measured at a fixed, masked exposure duration or noise level that is individually calibrated (typically at a level of 75-80% correct reports). What happens at other exposure durations is unclear. Starrfelt, Petersen, & Vangkilde (2013) aimed to explore the extents and limits of this effect, both for singly presented stimuli, and for multiple stimuli presented simultaneously. We thus designed two novel word superiority experiments, based on the Theory of Visual Attention (TVA)-framework (Bundesen, 1990; Habekost, 2015). The aim was to compare report of whole words vs. single letters both for singly presented stimuli (single item report), and in a whole report paradigm presenting six stimuli simultaneously, and also to quantify the effect of stimulus type. Using TVA-based methods, performance over a range of exposure durations can be analysed into different functional components, enabling us to decide if the word superiority effect is mainly reflected in the threshold for conscious processing (can words be seen at lower exposure durations than letters?), or in visual processing speed (are words processed faster than single letters?). In addition, we wanted to quantify the capacity of visual short-term memory (visual apprehension span) for words vs. letters, to see if words were treated as units in visual short-term memory.

The main findings were as follows: In a familiarisation task, measuring RTs to the included letter and word stimuli, we found that words were named faster than single letters. As mentioned above, this effect was observed by Cattell (1886a), but it has for some reason received little attention since. The effect was significant in 15/ 21 individual subjects, and highly significant on the group level. In the single item condition, where subjects had to identify a single letter or single word (in separate conditions) across a range of exposure

durations, the word-superiority effect was also readily detected. Indeed, on a group level, the effect was significant at all exposure durations above the perceptual threshold and until performance reached ceiling levels.

In the whole report paradigm, where six unrelated letters or six words were presented peripherally (at ~5 degrees), the findings were less clear. On one side, subjects did encode fewer words than single letters, indicating that words are not treated as units in visual short-term memory (in which case performance with letters and words should be equal). On the other hand, if one added up the number of letters in the words that were reported, this did exceed the number of independent letters that could be reported, which seems to indicate that words can be integrated to some degree even in the peripheral visual field.

4.3. From word superiority to word inferiority

Habekost, Petersen, Behrmann & Starrfelt (2014)

Having determined that the single item paradigm was suited to detect the word superiority effect even over a range of exposure durations, we wanted to investigate the word superiority effect in pure alexic patients once again. Habekost, Petersen, Behrmann, & Starrfelt (2014) thus used the single stimulus experiments (naming and single item report) from Starrfelt, Petersen et al. (2013) to address the hypothesis that parallel letter processing in pure alexia is reduced or abolished. If that is the case, then the patients should show no word superiority effect, but rather a "letter superiority effect" (i.e., they should perform better with single letters than three letter words). For the single item report experiment, the results were quite clear; none of the four patients tested showed a word superiority effect, but either performed at the same level for letters and words, or worse with words than letters. We suggested that this could be interpreted as a demonstration of a lack of parallel-processing abilities, impaired top-down enhancement of word processing (or both). The results, however, also revealed something more surprising: The single letter processing abilities of the patients were not predictably related to their word processing skills. This was particularly evident in patient SH, who performed within the normal range in reporting briefly presented letters, while he was severely impaired in reporting briefly presented words, and in naming letters and words. This pattern prompted us to perform a dissociation analysis (cf. section 2.1.1.), statistically comparing his performance with words and letters in

the single item report experiment. This analysis revealed that his pattern of performance reflected a classical dissociation between letter and word report (letter performance within the control range, word performance significantly different from controls, and a significant difference between the performance with letters and words as related to control performance). In addition, SH's visual letter processing performance was surprisingly different from his performance when naming the same letters (single letter report was 1.25 SD from the control mean, while his letter naming was extraordinarily slow at 9.4 SD from control mean). This, on one hand, does suggest that SH had problems at some levels of letter processing (just not in visual perception of the letter), but on the other hand, this finding clearly challenges the idea that a deficit in letter recognition is the cause of pure alexia. The pattern of performance observed in SH prompted us to directly compare the other three patients' performance with letters and words both in the RT task and the single item report task, and the findings were quite surprising; In all four patients performance with letters and words, in both tasks, were dissociated even for the patients who were also impaired in single letter processing. This suggests that the problems in word reading exhibited by these four patients cannot be (fully) explained by their processing limitations for single letters.

4.3.1. Single letter processing in pure alexia.

The question of whether the core processing deficit in pure alexia affects single letters or only arises with letter arrays has been debated for many decades (Farah, 2004; Kinsbourne & Warrington, 1962). A first answer to that question is that for patients with global alexia, the problem clearly affects recognition of single letters (Cohen & Dehaene, 2000; Dejerine, 1892; Larsen, Baynes, & Swick, 2004; Leff et al., 2001). The milder pure alexic patients are, however, often able to identify letters correctly, but do they do so normally? Behrmann & Shallice (1995) proposed that, "The default explanation for the functional deficit underlying pure alexia should be that of an impairment that results in less efficient letter processing, and alternative accounts (…) should be considered only when that hypothesis has clearly been found to be wanting" (p. 452) . In a comprehensive review of LBL-reading, Behrmann, Plaut et al. (1998) found "no single subject for whom letter recognition is definitively normal" (p.23), which led them to conclude that "a deficit in letter processing

(perhaps attributable to an even more fundamental perceptual impairment) is common to all LBL-readers" (p. 45-46). This is an important point: Even if all pure alexic patients have problems with letter processing, this does not mean that the cause of their reading problems lies in letter processing per se.

Also, the relationship between single letter processing and word reading is not straightforward. Shallice (1988) reported a correlation between reading speed and the accuracy of single-letter identification in a group of eight LBL-readers, which suggests a strong relationship between the two processes. However, others have described patients with fairly similar letter recognition patterns who nevertheless show very different performance in word recognition (Hanley & Kay, 1996).

In our review of number reading in pure alexia, we found ten cases of pure alexia/LBL-reading where letter identification was reported to be intact (Starrfelt & Behrmann, 2011). In all other cases (N=65), letter identification was reported to be impaired. Of the ten cases with reportedly intact letter recognition, data to support the claim was only reported for three patients (Caffarra, 1987; Rosazza et al., 2007; Warrington & Langdon, 1994; 2002). The remaining seven studies merely noted in the case description that letter and number reading was intact or at least accurate. The most convincing of these cases is a patient reported by Rosazza et al (2007). Their patient (FC) had reaction times within the normal range for both letter and digit naming, and was also within normal limits on letter identification with brief presentation. No accuracy scores are given for the letter and digit naming tasks, but assuming that accuracy was also within the normal range, this patient seems to have intact letter and digit identification skills. FC's RTs in word reading were mildly elevated, with a very modest word length effect of 70–90 ms per letter. He was also impaired in some non-reading, visual tasks. Rosazza et al.(2007) argue that FC has a deficit in integrating letters into letter groups and words, and that this deficit in itself is sufficient to give rise to pure alexia. This case is noteworthy because it may be the only one on record demonstrating normal RTs in both letter and digit naming in pure alexia, in spite of other visual deficits being present. So, although very rare, intact letter processing has been shown previously in at least one patient with pure alexia. This provides us with quite an explanatory challenge, if we are to seek a common explanation for the reading deficit in all patients with pure alexia.

An important point contributed by Rosazza et al. (2007), however, was that while the same explanation for the reading deficit may not hold for all patients with pure alexia, the key issue from a cognitive neuropsychological perspective is to explain the patients' deficits within the same model. Taking any model of the early reading process / visual word recognition as a starting point, then, it becomes obvious that lesions to different levels may give rise to the same observable symptom; a word length effect. Adding the classical assumption that the architecture of this system is shared between individuals, we then need to ask what type of architecture could give rise to the different deficits and dissociations observed in pure alexia. Traditionally, this type of localisation would be done within a box-and-arrow, relatively feed-forward prone system, and here perhaps lies one of the great challenges for research in visual word recognition; The visual system is a highly interactive system, with both lateral and top-down connections, and this makes it very difficult to draw firm inferences about this cognitive or neural architecture based on studies of (slightly) different patients. For our purposes, at least it seems clear that the relationship between letter and word processing (in pure alexia) is not as straightforward as indicated by earlier studies, and that the reading deficit need not include a problem with visual identification of single letters.

4.4. Word superiority in central and peripheral vision

Sand, Habekost, Petersen, & Starrfelt (2016).

One characteristic of pure alexic letter identification, that we had noticed in earlier studies, was that performance with centrally presented stimuli was disproportionally affected compared to peripherally presented stimuli: "It is peculiar, and was unexpected, that while the central, or foveal, processing speed of our controls far supersede their speed in the periphery of the visual field, NN's speed of processing for letters is similar in the two regions. (…) this pattern could point to a form of ''foveal amblyopia'', where shape perception is disproportionally impaired in the centre of the visual field" (Starrfelt et al., 2010; pp. 252-253). At that point, we merely noted the discrepancy, and suggested that the deficit in the central visual field was likely to be the most important one in causing the reading deficit in pure alexia.

Another issue relevant to the relationship between processing in the central and peripheral (parafoveal) visual field was raised by Starrfelt, Petersen et al. (2013). In this study, we found that letters were processed more efficiently than whole words in parafoveal vision, but we could not determine if this was due to the simultaneous presentation of many items at once, or if it could be explained by the peripheral stimulus presentation alone. Sand et al. (2016) set out to test this by running a word superiority experiment comparing central and peripheral presentation of single stimuli (words or letters). Building on Habekost et al. (2014), a main question was whether peripheral presentation would have a different effect on word compared to letter identification, which could be expected from previous studies (Jordan & Patching, 2004). We found that while both letter and word identification was reduced with peripheral presentation, word identification was disproportionally affected. Indeed, while the word superiority effect was clearly present with central presentation (a replication of Starrfelt, Petersen et al., 2013), the effect was eliminated or even reversed when stimuli were presented in parafoveal vision (~5 degrees). This was true regardless of whether subjects knew in advance where the stimulus would be presented. This pattern of performance of normal subjects in parafoveal vision closely resembled what we observed in pure alexic patients (Habekost et al., 2014), and we speculated that the same mechanism might reduce word recognition in peripheral vision and pure alexia (Sand et al., 2016). At least the results indicated that a general visual degradation (seeing stimuli in the peripheral field) could result in performance similar to pure alexia.

A similar hypothesis regarding visual (object) agnosia, was recently suggested by Strappini et al. (Strappini, Pelli, Di Pace, & Martelli, 2017). They suggest that visual agnosia can be explained by visual crowding, a phenomenon that is known to limit visual perception of complex objects (but not simple ones like single letters) in peripheral vision. We thus speculated that the disproportionate effect of peripheral viewing on normal word processing compared to single letter processing, and the reduced word superiority effect in central vision in pure alexia, might result from a similar cause - visual crowding - a hypothesis that remains to be empirically tested.

5. What is the role of the right visual field (defect)?

Petersen, Vangkilde, Fabricius, Iversen, Delfi, & Starrfelt (2016)

Most – but not all - patients with pure alexia have a visual field defect affecting either the entire right hemifield or the upper right quadrant. In our early investigation of the word superiority effect, we found that the presence of a visual field defect was related to the size of this effect (Starrfelt, Gerlach, et al., 2013). We speculated that this was because the patient with full fields (TJ) was able to see more letters without moving his eyes, while the hemianopic pure alexic patients can only see the left part of the word when fixating centrally. Some studies have addressed the contribution of the hemianopia to pure alexic reading by comparing patients with pure alexia to patients with the much milder *hemianopic alexia* (Leff et al., 2001; Pflugshaupt et al., 2009). In hemianopic alexia, word reading is impaired by a visual field defect only (and not concomitant word processing deficits as in pure alexia), resulting in mildly elevated word reading times and word length effects, and slowed text reading (Leff & Starrfelt, 2014; Sheldon, Abegg, Sekunova, & Barton, 2012). Interestingly, Starrfelt, Gerlach, et al. (2013) noted that although patient TJ showed the largest word superiority effect, he was not the best performing pure alexic patient in terms of RTs or WLE. In a previous study, we had found that TJs visual apprehension span was reduced in both visual fields, and as mentioned above, we suggested that this reduced span contributed to the reading deficit in pure alexia (Starrfelt et al., 2009).

In an attempt to further characterize the relationship between visual apprehension span, visual processing speed and reading, we (Petersen et al., 2016) tested the reading performance (RTs and word length effect) as well as processing speed and apprehension span for letters in eight patients with posterior stroke. The few previous (TVA-based) studies of apprehension span and processing speed in patients with lesions to extrastriate cortex had only tested patients with specific visual deficits (see Habekost, 2015; Habekost & Starrfelt, 2009, for reviews), including integrative agnosia (Gerlach, Marstrand, Habekost, & Gade, 2005), simultanagnosia (Duncan et al., 2003), and (pure) alexia (Duncan et al., 2003; Habekost & Starrfelt, 2006; Starrfelt et al., 2009; 2010). Petersen et al. (2016) selected patients based on lesion site (a stroke in the territory of the posterior cerebral artery), rather than by symptoms (e.g., reading deficits). Eight patients were included, four

with left hemisphere injuries (of which two had pure alexia) and four with right hemisphere injuries. The visual fields of all patients were also measured.

We had previously argued that impaired processing speed (perhaps particularly in the central visual field) and reduced apprehension span (which can only be reliably measured in the parafoveal or peripheral visual field) were both important in determining pure alexia (Starrfelt et al., 2009; 2010). However, as mentioned above, a dissociation was later shown between processing speed for single letters and words in the central visual field (Habekost et al., 2014). Petersen et al. (2016) contributed another piece of the puzzle: All patients who had reduced visual apprehension span in their right visual field also showed impaired reading *regardless of lesion lateralization and visual field defects.* Reassuringly, the two pure alexic patients did have reduced visual span in the right field (caused by visual field defects), but interestingly, one of them showed apprehension span within the normal range in the left visual field. This contradicts our earlier hypothesis that a general deficit in visual apprehension span is instrumental in causing pure alexia, and suggests that a reduction of information uptake the right visual field due to either blindness or reduced apprehension span is the key deficit.

6. Back to square one: Characterizing pure alexia

Starrfelt & Shallice (2014)

In 2013, I hosted an expert-symposium on pure alexia, where many of the core researchers concerned with pure alexia and neural mechanisms for visual word recognition (in Latin scripts) participated[2]. As a result of this symposium, a special issue of the journal *Cognitive Neuropsychology* on pure alexia was published, including contributions from many symposium participants. The last paper included in this dissertation is the introduction to this special issue, which I co-edited with Tim Shallice (who also contributed to organizing the symposium). In this paper, we briefly reviewed the progress made in the field of pure alexia research since the previous special issue of the same journal on this topic, published in 1998.

[2] The symposium is well documented in words and pictures here: http://gade.psy.ku.dk/2013_Pure_alexia_www/2013pure_alexia.htm

In this dissertation, and in my previous work on pure alexia, I have argued that it is important to consider only the truly 'pure' cases when trying to answer questions about the core deficit and the cerebral substrate of pure alexia. For one thing, this means that patients with writing deficits (agraphia) should not be taken into account, neither should patients with aphasia or general visual agnosia. However, when reviewing the literature on pure alexia it becomes evident that this does not characterize the literature well. Many (if not most) studies of "pure alexia" include patients whose deficits are not entirely pure (see Starrfelt & Behrmann, 2011, Table 1; Starrfelt, Ólafsdóttir, & Arendt, 2013: Tables 1-4 for overviews). Many studies take the word length effect as a proxy for pure alexia, and do not report data on other cognitive or language functions. Thus, while we (Starrfelt & Shallice, 2014) listed a set of core characteristics of pure alexia, we also suggested that this list might be used as a checklist for which functions to assess and describe, regardless of whether patients conform to a strict diagnosis of pure alexia or not. As long as both the core and the 'associated' deficits are well described and sensitively tested, such studies may still contribute to our understanding of (pure) alexia and visual word recognition. This could, perhaps, even serve as a starting point for investigations looking more broadly at the relationship(s) between performance in reading, writing, naming, and visual recognition of objects.

In the previous special issue on pure alexia, Max Coltheart (1998) listed seven questions about pure alexia (or LBL-reading, which was the term preferred at the time) that needed to be answered by future studies. In 2014, four of these were still highly debated, while the field seemed to have lost interest in the remaining three. I will end this dissertation by considering two of these questions, taking a slightly more speculative approach than Starrfelt & Shallice (2014).

6.1. Is the relevant impairment specific to the reading system or is it a more general visual impairment?

This is by far the most debated question related to pure alexia and the cerebral bases for visual word recognition (e.g., Behrmann & Plaut, 2013; Dehaene & Cohen, 2011; Gaillard et al., 2006; Pflugshaupt et al., 2011; Price & Devlin, 2011; Roberts et al., 2013; Warrington & Shallice, 1980; Yong, Warren, Warrington, & Crutch, 2013). One of the reasons

this question has been difficult to address, is that most papers on pure alexia present only one or very few patients, and studies are hard to compare across languages, labs, and experimental paradigms. So for each demonstration of a patient with (seemingly) related deficits in general visual tasks and word recognition, there has been another patient with a (seemingly) selective deficit in word reading. Typically these patients are not tested on the same tests and experiments, or even diagnosed using the same criteria (some weigh LBL-reading but do not assess writing, others assess writing but do not test for visual deficits etc.), which makes it difficult to reach a firm conclusion applicable to all patients with pure alexia even when considering the literature on this topic as a whole.

One criticism raised against the "general visual impairment"-hypothesis is that it is underspecified (Yong et al., 2013), and thus hard to falsify. Perhaps this is true for some versions of this hypothesis, but there are also exceptions where specific predictions can be derived from such hypotheses. This is true for the "spatial frequency sensitivity"-hypothesis (Fiset, Gosselin, et al., 2006; Roberts et al., 2013) and (at least parts of) the recent many-to-many hypothesis (Behrmann & Plaut, 2013, 2014). Even our "too little too late"-hypothesis (Starrfelt et al., 2009) may fall in this category. At least we speculated about the mechanism relating the general deficits in speed and span to the reading deficits, and it should be clear from this dissertation that not all our predictions necessarily hold true for all patients.

If we sum up the data from the pure alexic patients presented in this dissertation, at least one of the patients have normal performance in at least one of the following visual tests / functions: visual field test; spatial frequency detection and discrimination; letter identification or naming; visual apprehension span in the left visual field. If every single patient may contribute to the understanding of the general syndrome, this seems to rule out many general visual or low-level explanations of pure alexia, perhaps including our own "too little too late" hypothesis. Rather, it seems to indicate that if there is a core common deficit across all patients, it is a "deficit in word recognition itself " which has the result that "even letters in familiar words suffer some of the same processing competition as unrelated display elements" (Duncan et al., 2003, p. 699).

But is this apparent "deficit in word recognition itself" really word specific, in the sense that it is caused by impairment in a word processing module or system? This remains unanswered by the present collection of papers. Note, however, that pure alexic reading patterns, including the disproportional impairment with words compared to single letters,

can be seen even in normal subjects when just a slight manipulation of moving the words away from fixation is done (Sand et al., 2016). Similarly, Fiset et al. (2006) elicited elevated RTs and WLEs of similar size to pure alexic patients in normal controls, when certain spatial frequencies were filtered out of word stimuli. Thus, simple, low-level visual manipulations do seem able to make "letters in familiar words suffer some of the same processing competition as unrelated display elements", and may lead to pure alexia like reading.

It should be clear, however, that even if pure alexia may be explained by a visual deficit, it is one that has a disproportional effect on word reading compared to other visual stimuli, an aspect that at least some proponents of the visual account have considered (Fiset, Gosselin et al., 2006; Starrfelt et al., 2009; 2010). Many patients with visual deficits do not have pure alexia. This is evident in patients with hemianopic alexia (Leff et al., 2001), in visual deficits following right hemisphere lesions like prosopagnosia (Hills, Pancaroglu, Duchaine, & Barton, 2015; Susilo, Wright, Tree, & Duchaine, 2015), and in disorders affecting the dorsal stream more than the ventral stream of visual processing (e.g., Balint's syndrome; Baylis, Driver, Baylis, & Rafal, 1994). In a study addressing this issue directly, Yong et al. (2013) reported normal word reading in two patients with severe visual deficits resulting from posterior cortical atrophy. They conclude that a general visual deficit does not necessarily lead to pure alexia, and claim that this challenges the general visual deficit hypothesis of pure alexia. Yong et al. (2013) go on to specify which visual mechanism(s) might lead to visual reading deficits. In line with my statement above, they write: "we would wish to state unambiguously that we are not denying that some forms of visual impairment may have an inevitable cost for reading function. Rather we would argue against (i) the pejorative and under-specified use of terms such as 'general visual impairment', and (ii) the assumption that *any* form of visual impairment can cause reading impairment. We have previously proposed that visual crowding (the excessive integration of visual features, sometimes referred to as lateral masking) may be one of several specific visual deficits which can cause a particular form of dyslexia" (Crutch & Warrington, 2007, 2009)" (Yong et al., 2013; p. 2304).

Crutch & Warrington (2007) report foveal crowding effects in patients with posterior cortical atrophy, and suggest that crowding is a key impairment in the reading deficit observed in these patients. Supporting this, Yong et al. (2016) showed in a longitudinal study that an increase in crowding over time lead to a deterioration of reading abilities in two patients with posterior cortical atrophy (the same patients who initially read normally, Yong

et al., 2013). It is unclear whether the reading deficits in these patients and patients with pure alexia have the same cause. It is intriguing, though, that the same mechanism (foveal crowding) has been suggested to account for reading problems in posterior cortical atrophy (Yong et al., 2016) as well as the visual recognition problems seen in visual (object) agnosia (Strappini et al. (2017). In our study of the word superiority effect in peripheral vision, we also speculated that visual crowding may limit word processing in normal peripheral vision and that a similar mechanism may be involved in pure alexia (Sand et al., 2016). This hypothesis remains to be tested. There is of course also the possibility that pure alexia may arise for different reasons in different patients, which leads to the next question asked by Coltheart (1998):

6.2. Is the disorder a homogeneous one?

The answer to this question is not clear and is partially a question of definition. Early on in the cognitive neuropsychological study of reading disorders, "fractionation" of syndromes were common. In the early literature, it was suggested that one should distinguish between Type 1 and Type 2 pure alexia (Hanley & Kay, 1996; Patterson & Kay, 1982), but the distinction never caught on. Others, myself included, have aimed to find an explanation that applies to all patients with pure alexia. This is the main reason for arguing that only the truly pure alexic patients should be studied to address this question. However, even if we include only those patients that live up to the diagnostic criteria suggested by Starrfelt & Shallice (2014), the answer is still not clear. Patients with pure alexia certainly have some things in common, like impaired reading, intact writing and language, no profound visual agnosia or dementia, and lesions in the posterior left hemisphere. On the other hand, patients show different degrees of impairment with letters and words, and widely different RTs and word length effects (Barton et al., 2014). Pure alexic patients also show different patterns of associated deficits: Some have problems with certain spatial frequencies (Roberts et al., 2014), some have problems recognizing faces (Roberts et al., 2014; Behrmann & Plaut, 2014) and / or objects (Starrfelt et al., 2009; 2010; Mycroft et al., 2009), many, but not all, have visual field defects that may affect their performance both in reading and non-reading tasks (Leff et al, 2001; Pflugshaupt, 2009; Starrfelt, Gerlach et al., 2013), but notably not all patients have all these deficits.

What does this mean, then? First of all, it means that finding *the* cause of pure alexia on a cognitive level may be impossible. But perhaps that should not be our goal. Going back to the early foundations of cognitive neuropsychology, group studies were abandoned to leave room for single case studies precisely because no two patients are exactly alike following brain injury. Just like no one is exactly identical before their injury. Although this is a trivial point, it might have been underestimated in the research on pure alexia. This may be particularly problematic because reading is an acquired skill in which people have different degrees of fluency even when their brains are functioning normally. Very early in the history of cognitive neuropsychology, Max Coltheart wrote that the usefulness of alexic syndromes to cognitive models of reading "is likely to be short-lived" (Coltheart, 1984, p. 370, cited in Coltheart, 2001). This prediction has not held true, but perhaps it should have. Based on reasoning from cognitive neuropsychology, we need not group patients according to symptoms to be able to use their performance to inform models of reading. In the words of Coltheart:

"(…) if a dyslexic syndrome is a specific pattern of preservations and impairments of reading… and if a modular theory of reading is appropriate, it follows that there are many different possible dyslexic syndromes. Any unique pattern of impairments (…) will produce a unique syndrome (…)

"The generalizations do not take the form of claiming that there exists a single syndrome which many patients exhibit. Instead these generalizations take the form of (…) a single theory (..) which can offer interpretations of the various sets of symptoms exhibited by different patients."

Although I do not subscribe to a strictly modular theory of reading, I do think Coltheart raises an important issue, and that models are important for our understanding of impaired and preserved reading. And here lies a great challenge for pure alexia research; the model or theory to explain the observed performance is underspecified, and indeed, it seems a daunting task to come up with a theory or model to explain all the patterns of preserved and impaired performance that has been observed in pure alexia. Instead, much of the debate to date has revolved around the relative selectivity of the syndrome and rather broad questions related to this.

7. Closing remarks

Perhaps some of the questions asked in this dissertation are on the verge of being theoretically outdated. We used to think about the brain and cognition as being digital phenomena – either there or not, either selective or not. But if one views the brain – and the cognitive system – as made up of distributed processing mechanisms that are susceptible to learning, this has consequences for the questions we ask and the methods we use to answer them. This is one of the most important challenges for cognitive neuropsychology in general, and the study of reading in particular (e.g., Price, 2018).

If a model of pure alexia based on peripheral vision is fruitful, and crowding turns out to be a central impairment in pure alexia (Sand et al., 2016), the question about why words – which in normal readers "escape crowding" – become susceptible to crowding in pure alexia will still remain. Regardless of how many well designed tests of word and visual processing are employed in the study of pure alexia, there always seems to be room for "an additional deficit in word recognition itself" (Duncan et al., 2003). A deficit that is a likely candidate for being the core deficit in pure alexia, if there is one. It seems that the "glue" that binds words together so that they are processed fast, automatically, and efficiently, is gone or degraded. This glue may be fast parallel letter processing (bottom up), lexical effects (top-down), letter integration (as a word specific or general process), or a combination of these. This question remains unanswered by the present dissertation.

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Dansk resume af afhandlingen

Emnet for denne afhandling er læseforstyrrelsen ren aleksi, som ses efter skader bagtil i venstre hjernehalvdel. Patienter med ren aleksi har inden skaden kunnet læse normalt, men efter skaden læser de langsomt og besværet, og de udviser en ordlængdeffekt; jo flere bogstaver et ord består af, des længere tid tager det dem at læse det. Sproget i øvrigt er ikke påvirket; patienterne kan stadig tale, forstå, og faktisk også skrive. Denne introducerende tekst beskriver de centrale fund fra de 9 artikler, som afhandlingen er baseret på, og indeholder således en sammenfatning og diskussion af litteraturen om ren aleksi og de eksperimentelle studier, jeg har foretaget for at belyse syndromet. Herunder er der studier af grundlæggende visuelle processer i ren aleksi, af patienternes evne til at læse bogstaver, tal, og ord, samt to eksperimentelle studier af ordgenkendelse hos normale, der søger at belyse det centrale spørgsmål: Hvad er den grundlæggende forstyrrelse i ren aleksi? Spørgsmålet forbliver ubesvaret, men enkelte hypoteser afvises som usandsynlige. Afslutningsvis foreslås en ny forklaring på ren aleksi, der forsøger at sammenfatte såvel litteraturen på området som de rapporterede eksperimentelle fund.